NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY EVALUATION

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Contents:

The following documents are made available to consultees and commentators:

Final Scope and Final Matrix of Consultees and Commentators

1. **Company submission** from Orchard Therapeutics

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   - ArchAngel MLD Trust
   - MLD Support Association UK
   - Mucopolysaccharide Society

4. **Expert personal perspectives** from:
   - **Prof. Paul Gissen – clinical expert**, nominated by Orchard Therapeutics
   - **Dr. Simon Jones – clinical expert**, nominated by Orchard Therapeutics, ArchAngel MLD Trust, Alex, The Leukodystrophy Charity, MLD Support Association UK and The MPS Society
   - **Dr. Rahul Singh – clinical expert**, nominated by British Paediatric Neurology Association (BPNA)
   - **Nicola Elson – patient expert**, nominated by ArchAngel MLD Trust, MLD Support Association UK and The MPS Society
   - **Georgina Morton – patient expert**, nominated by ArchAngel MLD Trust, Alex, The Leukodystrophy Charity, MLD Support Association UK and The MPS Society
   - **Sophie Thomas – patient expert**, nominated by ArchAngel MLD Trust, Alex, The Leukodystrophy Charity, MLD Support Association UK and The MPS Society
   - **Ayesha Ali – NHS England commissioning expert**, nominated by NHS England

5. **Evidence Review Group report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

6. **Evidence Review Group report – factual accuracy check**

7. Company response to Evidence Review Group clarifications following factual accuracy check

8. Evidence Review Group report addendum (post ECM1)

9. Company additional evidence

10. ERG critique company additional evidence

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

OTL-200 for treating metachromatic leukodystrophy

[ID1666]

Company submission of evidence

February 2020

Contents

List of tables

List of figures

Glossary of terms

AAA	Anti-ARSA antibodies
ACP	Abnormal clonal proliferation
ADA-SCID	Adenosine deaminase severe combined immunodeficiency
ADR	Adverse drug reaction
AE	Adverse event
aHUS	Atypical haemolytic uremic syndrome
ALT	Alanine transferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ARSA	Arylsulfatase A
ARSA LVV	Transduced with a lentiviral vector
AWMSG	All Wales Medicines Strategy Group
BAER	Brainstem auditory evoked response
BIA	Budget impact analysis
BM	Bone marrow
BSC	Best Supportive Care
CASP	Adapted from Critical Appraisal Skills Programme
cDNA	Complementary deoxyribonucleic acid
CDP	Clinical development programme
CEA	Cost-effectiveness analysis
CFH	Complement factor H
CHMP	Committee for Medicinal Products for Human Use
CI	Convidence interval
CNS	Central nervous system
COI	Cost of illness
COMFORT	Caregiver Observed Metachromatic Leukodystrophy Functioning and Outcomes Reporting Tool
CRF	Case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate use programme
DBS	Deep brain stimulation
DNA	Deoxyribonucleic acid
DP	Drug product
DQ	Developmental quotient
DQp	Developmental Quotient – Performance
EAP	Expanded access programme
eCRF	Electronic case report form
EJ	Early Juvenile
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMA	European Medicines Agency
ENG	Electroneurography
EQ-5D	EuroQol five-dimension scale questionnaire
ES	Early-symptomatic
ES EJ	Early-symptomatic Early Juvenile
EU	European Union
FDA	United States Food and Drug Administration
FDA	United States Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor
G-tube	Gastrostomy

GLIA	Global Leukodystrophy Initiative
GMFC	Gross Motor Function Classification System
GMFC	Gross motor function classification
GMFC-MLD	Gross Motor Function Classification MLD
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
GMFM	Gross Motor Function Measure
GP	General practitioner
GT	Gene therapy
GvHD	Graft-versus-host-disease
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCRU	Healthcare resource use
HE	Hospital Exemption
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQL	Health-related quality of life
HSCT	Allogeneic haematopoietic stem cell transplantation
HSPC	Haematopoietic stem and progenitor cells
HST	Highly specialised techologies
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IDS	Integrated data set
IP	Indicated population
IQ	Intelligence quotient
ISS	Integrated Safety Set
IT	Intrathecal
IU	Units
IV	Intravenous
J-tube	Jejunostomy
JACIE	Joint Accreditation Committee ISCT-Europe & EBMT
KOL	Key opinion leader
LI	Late Infantile
LJ	Late Juvenile
LS	Least square
LSD	Lysosomal storage disease
LV	Lentivirus
LV+	LV-transduced
MAA	Managed Access Agreement
MAC	Myeloablative conditioning
MCP	Membrane cofactor protein
MDS	Myelodysplastic syndrome
MLD	Metachromatic Leukodystrophy
MNC	Mononuclear cells
mPB	Mobilised peripheral blood
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NBS	New-born screening
NCI	National Cancer Institute
NCV	Nerve conduction velocity
NHS	National Health Service
NHSBT	NHS Blood and Transplant Service
NHx	Natural history
NIH	National Institutes of Health
NNH	Number needed to harm
NNT	Needed to treat
OS	Overall survival
OSR-TIGET	Ospedale San Raffaele - Telethon Institute for Gene Therapy
OTL-200-c	Cryopreserved formulation of OTL-200

OTL-200-f	Fresh formulation of OTL-200
OTL-MM	Orchard Therapeutics (Europe) Ltd Medical Monitor
PAG	Patient Advisory Group
PAS	patient access scheme
PB	Peripheral blood
PBMC	Peripheral blood mononuclear cells
PBRER	Periodic Benefit-Risk Evaluation Reports
PCR	Polymerase chain reaction
PD	Pseudodeficiency
PEG	Percutaneous endoscopic gastrostomy
PIND	Progressive intellectual and neurological deterioration
PNS	Peripheral nervous system
PS	Pre-symptomatic
PS EJ	Pre-symptomatic Early Juvenile
PS LI	Pre-symptomatic Late Infantile
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCL	Replication competent lentivirus
RCT	Randomised controlled trial
rhARSA	Recombinant human arylsulfatase A
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
sCMFS	Severe cognitive and motor impairment-free survival
SD	Standard deviation
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SMAC	Sub-myeloablative conditioning
SMC	Scottish Medicines Consortium
sMFS	Severe motor impairment or death
SmPC	Summary of Product Characteristics
SOC	System organ class
SPC	summary of product characteristics
TA-TMA	Transplant-associated thrombotic microangiopathy
TB	Tuberculosis
TIGET	Telethon Institute for Gene Therapy
TTO	Time Trade-Off
ULN	Upper limit of normal
VAS	Visual analogue scale
VCN	Vector copy number
VEP	Visual evoked potential
VOD	Veno-occlusive disease
VSV-G env	Vesicular stomatitis virus
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

Executive Summary

1. Nature of the condition

Metachromatic Leukodystrophy (MLD) is an ultra-rare, fatal inherited and devastating neurodegenerative genetic condition that has a rapid and predictable trajectory of progression. The course of the disease is neurodegenerative, with developmental stagnation, followed by the loss of abilities in motor function, language and cognition. (Kehrer et al., 2020) [Section 6.1]

MLD is caused by mutation in the *ARSA* gene that leads to deficient activity of ARSA enzyme (van Rappard et al., 2015). ARSA deficiency causes accumulation of sulfatides in the nervous system leading to microglial damage, progressive demyelination and neurodegeneration. After initially developing normally, children with MLD can rapidly lose their acquired speech, cognitive and motor skills, and the ability to feed themselves and safely swallow. They become bedridden and completely dependent on parents and caregivers before eventually losing their lives. [Section 6.1]

The MLD disease spectrum can present in a variety of clinical forms, primarily based on the age of onset of the first symptoms. The disease is classified into four main clinical phenotypes and it is well known that the underlying disease pathophysiology is common for all phenotypic forms of MLD (Biffi 2008a). [Section 6.1]

- Late Infantile (LI) MLD (onset before age 30 months) is the most aggressive form of the disease, showing a highly predictable and severe disease course, characterised by a relentlessly progressive decline in motor and cognitive function and an early death. The 5-year survival after onset is 25% and the 10-year survival is zero (Mahmood et al 2010)

- Early Juvenile (EJ) MLD presents with symptom onset between the ages of 30 months and 6 years of age. EJ patients tend to have a slower and more protracted initial disease progression than LI patients. However, once symptoms occur, they can progress rapidly, and once patients lose the ability to walk independently disease progression occurs at the same rate as in LI patients.
- Late Juvenile (LJ) MLD presents with symptom onset between 7 years and 16 years of age.
- Adult MLD patients develop symptoms from 17 years of age.
- LJ and adult MLD patients predominantly develop cognitive and behavioural symptoms that can precede the deterioration of motor function and have more prolonged, less rapid disease progression compared to LI and EJ patients (Biffi, 2008a; Biffi 2008b; Gieselmann, 2010).

There is currently no approved disease-modifying treatment for MLD; available treatments only treat the symptoms of the disease and none of them address the underlying cause of disease nor have been proven to slow disease progression or prevent the fatal outcome. [Section 8.2]

The birth prevalence of MLD has been estimated as 6.8 per million live births in the UK (Stellitano et al. 2016). Based on 640,370 live births in England and Wales in 2019 (ONS 2019), about 4–5 MLD patients would be born every year, of which approximately [redacted] patients annually would be expected to be eligible for treatment with OTL-200. [Section 6.1]

2. Impact of the new technology

Overview of the technology

OTL-200 is an *ex vivo* genetically modified autologous $CD34^+$ haematopoietic stem and progenitor cell gene therapy that will be administered as a cryopreserved dispersion for infusion that corrects the genetic defect in MLD patients. Autologous $CD34^+$ haematopoietic stem and progenitor cells (HSPCs) are collected from patient bone marrow (BM) harvest or from peripheral blood (PB) and transduced with a lentiviral vector (ARSA LVV),

which inserts one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) directly into the cell's genome. [Section 2.2]

These genetically modified stem cells produce ARSA enzyme at supraphysiological levels, that can subsequently be taken up by surrounding cells in the body and migrate through the blood-brain-barrier to the brain and engraft in the central nervous system (CNS). Following successful and stable engraftment in the patient, the effects of OTL-200 are expected to persist throughout the lifetime of the patients due to the self-renewing properties of gene corrected HSPCs. [Section 2.2]

OTL-200 is composed of one or more infusion bags containing a dispersion of 2-10 x 10^6 cells/mL of the patient's own stem cells which have been corrected and suspended in a cryopreservative solution. By utilising the patient's own stem cells, the risks of graft-versus-host disease associated with allogeneic HSCTs are circumvented. [Section 2.3]

Population

The intended indication (as reflected in the positive CHMP opinion) for OTL-200 is the treatment of MLD characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of ARSA enzymatic activity:

- in children with Late Infantile or Early Juvenile forms, without clinical manifestations of the disease,
- in children with the Early Juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline [Section 1]

Comparators

The comparator, best supportive care (BSC), reflects current clinical practice in the UK. It aims to manage disease complications and support quality of life as far as possible, but does not target the root cause of the progressive motor and cognitive decline or halt progression of the disease. Current supportive therapies include physical therapy to maintain mobility, muscle relaxant medications to reduce spasticity, pain management, management of skeletal

deformity, respiratory physiotherapy to manage pulmonary infections, anti-convulsant drugs to control seizures, and anti-psychotic medications to control psychiatric symptoms, as well as dietary support, enteral nutrition through a feeding tube in cases of dysphagia, and family and psychological counselling. (Gomez-Ospina, 2006) [Section 8.1]

Although allogeneic haematopoietic stem cell transplantation (HSCT) has previously been used in the treatment of MLD, it is mainly reserved for patients with LJ and adult variants who would not be eligible for OTL-200 treatment as per the current indication. Therefore, it is not considered as a comparator for this submission; a view shared by UK MLD experts (n=6) who have stated that allogeneic HSCT would not be used routinely to treat the OTL-200-indicated patients even in a world without a gene therapy option. (Orchard Data on file, 2020) [Section 8.1]

Clinical effectiveness and safety of OTL-200

The safety and efficacy of OTL-200 has been demonstrated in a comprehensive clinical programme involving 35 patients with up to 8 years of follow-up who were treated in two clinical studies (the registrational study 201222 and the clinical study 205756) and three Expanded Access Programs (EAPs). [Section 9.4]

- 29 of the 35 patients in the clinical programme were treated with the fresh formulation of OTL-200 (OTL-200-f) and six patients treated with the commercial cryopreserved formulation (OTL-200-c).
- The fresh formulation data include 20 patients treated in registrational study 201222 and 9 patients treated in three EAPs. Registrational Study 201222 and the EAPs have a similar study design and were conducted by the same team at the same centre, and these patients have been combined to make an integrated data set (IDS; n=29).

This submission includes efficacy data from a post-hoc analysis of data from the subset of patients in the integrated data set that would be eligible for treatment as per the approved CHMP positive opinion indication. In total [redacted] patients in the integrated data set were included in this analysis:

[redacted] patients with pre-symptomatic Late Infantile (PS LI) MLD, [redacted] patients with pre-symptomatic early juvenile (PS EJ) MLD and [redacted] patients with early-symptomatic early juvenile (ES EJ) MLD (hereafter referred to as the indicated population). [Section 9.4]

The [redacted] patients in the integrated data set are not included in the post hoc efficacy analysis as they would not be eligible for treatment based on the indication which received positive opinion from the CHMP. [Section 9.4]

In addition, preliminary efficacy data from the six patients treated with the commercial cryopreserved formulation is also included in this submission to demonstrate the *in vivo* comparability with the fresh formulation. [Section 9.4]

To provide a comprehensive overview of the safety of OTL-200, the safety data presented in this section are from all patients in the clinical programme (i.e. all 29 patients treated with OTL-200-f and the six patients treated with OTL-200-c). [Section 9.4]

As none of the studies had a control arm, due to ethical and practical reasons of treating a fatal and potentially rapidly progressing disease like MLD, the studies used data from age and disease subtype-matched patients in the NHx study run by the same centre (OSR-TIGET) as a comparator group. Analysis using data from untreated affected siblings in the NHx study were also undertaken. [Section 9.4]

Summary of Efficacy Data from Indicated Population

The data from the indicated population analysis, show that OTL-200, provides meaningful clinical benefits in the treatment of PS LI, PS EJ and ES EJ patients. [Section 9.6]

1. Engraftment:

Durable and stable peripheral engraftment of gene-corrected cells was observed from 1 month post OTL-200 administration in all subjects treated, as indicated by percentage Lentiviral vector-positive (%LV+) cells well above the protocol-defined target of 4% and persistent vector copy number (VCN) in $CD34^+$ cells isolated from the BM and PB throughout the

follow-up period of and have remained stable throughout the duration of the follow-up (up until 8 years in some patients).

These findings demonstrate a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting microglial reconstitution and the long-term production of ARSA.

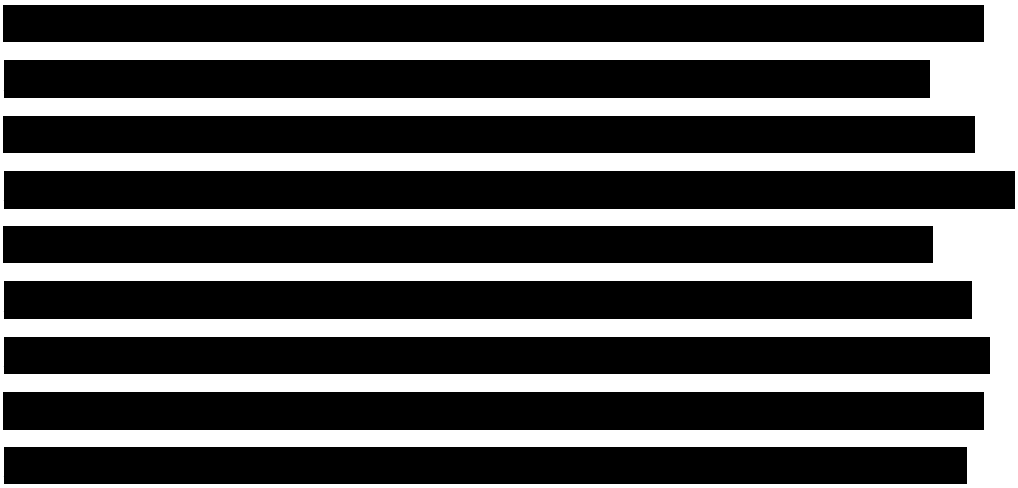
2. **ARSA activity:**

Reconstitution of ARSA activity in the haematopoietic system and CNS was observed in all subjects in the indicated population, with ARSA levels in PBMCs and CSF reaching values within the normal reference range by 3 months post-treatment and remained stable within or above the normal range throughout the duration of the follow-up.

These results provide indirect evidence that genetically modified cells, effectively migrated to the CNS, engrafted, and produced ARSA enzyme activity within or above the normal range.

3. **Gross Motor Function:**

When compared to age-matched natural history (NHx) patients within the same disease subtype, PS LI, PS EJ and ES EJ MLD subjects treated with OTL-200 showed normal motor development, stabilisation, or delay in the rate of progression of motor dysfunction as measured by GMFM total score (%).



Gross motor function results assessed by GMFC-MLD were consistent with GMFM results. In summary, all OTL-200 treated patients in the

indicated population, either stabilised at the same GMFC score throughout the follow-up period or had a slower decline in GMFC score compared to age-matched NHx patients or the matched siblings.

4. **Cognitive function:**

Developmental quotient (DQ) and age equivalent scores were used as exploratory analyses of cognitive function and provide further evidence that the high levels of engraftment and enzymatic reconstitution translate into relevant treatment effects on key domains that are hallmarks of MLD.

[redacted]

Age-equivalent scores showed normal acquisition of cognitive skills in the majority of treated LI and EJ subjects at chronological ages at which untreated NHx subjects showed severe cognitive impairment.

5. **Overall survival (OS):**

Analysis of overall survival suggests that treatment with OTL-200 improves overall survival in PS LI MLD compared with untreated patients and matched siblings. [redacted]

[redacted]

6. Composite quality of life-adjusted survival endpoints:

Given the advances in supportive care, patients are now able to survive for many years in an advanced stage of the disease with supportive care (Mahmood et al., 2010). As such overall survival results may be confounded by different approaches of families and health system to supportive care whilst in the advanced stages of disease. To address these, quality-adjusted survival analyses involving a composite endpoint of time to severe motor impairment or death was conducted.

Results from analyses of severe motor impairment-free survival (sMFS) demonstrate that subjects treated with OTL-200 prevents or delays progression to the advanced stage of disease and early death.

[redacted]

Summary of Efficacy Data from patients treated with OTL-200-c

Preliminary clinical data from Study 205756 support the comparability between the fresh and commercial cryopreserved formulations of OTL-200. [Section 9.6]

Peripheral engraftment of gene-corrected cells was observed from 1 month in all subjects treated with OTL-200-c. The %LV+ transduced cells and VCN values were within the range observed in subjects treated with the fresh formulation. Similarly, ARSA activity profiles in PBMCs and CSF were consistent with results observed in subjects treated with the fresh formulation.

This clinical experience with the fresh product strongly indicates that patients treated with the cryopreserved formulation will achieve similar clinical outcomes to those observed in patients treated with the fresh formulation.

Summary of safety data from all patients in the clinical programme

OTL-200 was well-tolerated with no treatment-related serious adverse events in patients treated with either the fresh or cryopreserved formulations of OTL-200. The most common adverse events observed were consistent with the known safety profile of busulfan, symptoms of MLD, or events expected during childhood. [Section 9.7]

There were three deaths in the clinical programme, none of which were related to OTL-200. Two of the deaths occurred in patients who would be ineligible for treatment per the approved CHMP indication. The other death was due to ischemic cerebral infarction and considered unrelated to OTL-200 or MLD.

In conclusion, the safety findings in subjects treated with OTL-200 are in line with what would be expected in subjects who have undergone busulfan conditioning and haematological reconstitution.

3. Cost to the NHS and Personal Social Services

The list price of OTL-200 in England is [redacted] per treatment. A simple discount patient access scheme (PAS) with a price of [redacted] per treatment has been submitted to the NHS. The net budget impact with the PAS price is estimated to be [redacted]. These figures incorporate the cost offsets in healthcare resource use expected with treatment with OTL-200.

This does not exceed the budget impact threshold of £20 million in any of the first 3 years. The budget impact of OTL-200 in any of the first five years of commercialisation, represents [redacted] of the NHS budget for specialised services of approximately £16.6 billion. [Section 12.3]

4. Value for money, including incremental QALYs and incremental cost per QALY as per company base case

A *de novo* cost-effectiveness analysis of treatment with OTL-200, in comparison to best supportive care (BSC), was conducted for patients with Late Infantile or Early Juvenile MLD, in line with the NICE scope and interim methods for manufacturers and sponsors. [Section 12.1]

A number of key assumptions were made related to the duration of clinical benefit of OTL-200, MLD patient progression between GMFC-MLD and cognitive stages, and time to engraftment of OTL-200. These assumptions were further validated by expert clinical opinion or sourced from a structured expert elicitation process. The impact of these assumptions was also explored in several sensitivity and scenario analyses.

Costs and resource use were identified through a structured expert elicitation process and were implemented from an NHS/PSS perspective. Wherever cost information was not available, expert clinical opinion was used to inform the assumptions used for these inputs.

For the combined MLD population (comprising all variants within the indication: PS LI, PS EJ and ES EJ), the base case analysis indicated that OTL-200 is associated with incremental gains of [redacted] QALYs and [redacted] life years versus best-supportive care (at a discount rate of 1.5%). The corresponding base case ICER is [redacted] per QALY gained for OTL-200 versus best supportive care based on the PAS price. [Section 12.5]

A number of scenario and sensitivity analyses have been conducted to assess the impact on the base case ICER. Scenario analyses included varying the parameter values for the discount rate, full-responder status, progression modifiers, caregiver disutilities, distributions of the underlying MLD disease cohorts in the combined population, and alternative natural history data sources. The majority of the scenario analyses demonstrated similar conclusions to the base case analysis, with ICERs at the PAS price in the range of [redacted] per QALY gained versus best supportive care. [Section 12.5]

Subgroup analyses of each of the underlying disease variants (PS LI, PS EJ and ES EJ) indicated that OTL-200 was cost-effective in the pre-symptomatically treated population (determining ICERs of [redacted] per QALY gained for PS LI and [redacted] per QALY gained vs BSC for PS EJ), and also in the ES EJ population with an ICER of [redacted] per QALY gained vs BSC at the PAS price of OTL-200. [Section 12.6]

Deterministic sensitivity analyses show that the top three important parameters in the model affecting the model outcomes are the proportion of ES EJ Partial Responder OTL-200 patients stabilising at GMFC 2, and the percentage of OTL-200 PS EJ and PS LI Full responders (Sections 12.5.11 and 12.5.14). Choice of perspective and caregiver disutility had a minimal impact on the modelled outcomes. [Section 12.5]

In summary, the results from the cost-effectiveness analysis are substantially lower than the HST cost per QALY thresholds, indicating that OTL-200 would be a cost-effective therapy in England and Wales.

5. Impact of the technology beyond direct health benefits

In addition to providing direct clinical benefits to the patient, OTL-200 is anticipated to benefit families and caregivers by improving wellbeing and reducing time spent caring as the emotional impact for caregivers stems from loss of identity, poor self-care, feeling unable to help their child can lead to anxiety, depression, and some shifts in family dynamics including spousal conflicts. These benefits in turn will also lead to savings in government departments other than the NHS including those for education and social security. [Section 14]

A reduction in the length and intensity of caring may also reduce the risk of mental health problems and family difficulties. Therefore, OTL-200 will impact several key factors of family life including: (i) The emotional and psychological well-being of caregivers and their families; (ii) The ability to build normal relationships with family, friends and social relationships; (iii) The education and social interaction of the affected children who have a chance to grow up and lead normal lives; (iv) Work productivity gains for parents/caregivers and

ability to pursue career ambitions; (v) Family finances and outside sources of financial support, including friends. [Section 14.1]

These additional benefits to health system and society in general (including family members beyond the main caregiver) have not been included in the cost-effectiveness and budget impact model. Therefore, the presented cost-effectiveness and budget impact figures for OTL-200 are conservative estimates. [Section 14.3]

The impact of the technology on the delivery of the specialised service

OTL-200 would be administered in a very small number (1-2) of specialised LSD treatment centres in U.K. The introduction is not expected to change the treatment care pathway or lead to service reconfigurations. Rather it would enable these centres to gain significant additional experience in using their established infrastructure to deliver *ex vivo* gene therapies particularly for neurological conditions which could then be applied for future treatments for other diseases and conditions. [Section 14.6]

Orchard Therapeutics is committed to investing in further research in this area. As part of its commitment to European regulators, the manufacturer is planning a long-term follow-up study that will collect further clinical data on patients treated with OTL-200 over a 15-year period. In addition, Orchard Therapeutics is working in collaboration with other stakeholders on a number of initiatives including the disease awareness and early diagnosis / newborn screening pilot study designed to lead to early diagnosis of MLD patients, which would translate into improved outcomes and overall cost-effectiveness of OTL-200. [Section 14.5]

6. Conclusions

In summary, the clinical data to date has shown that OTL-200 provides meaningful clinical benefits in the treatment of children with PS LI, PS EJ and ES EJ by preserving cognitive function, delaying time to severe motor disability and slowing down brain demyelination and atrophy. Most children treated with OTL-200 have shown normal development of motor function and cognitive skills (out to 8 years currently), sustaining the time during which they are comfortable and alert and allowing them to develop and maintain daily

activities of living, such as walking and self-feeding, and build normal relationships with family members and carers.

The cost-effectiveness analysis found that OTL-200 offered significant gains of life years and QALYs to patients, and reduced the time spent in more severe stages of disease progression. Scenario analyses tested a wide range of assumptions employed in the base case analysis, including progression rates, starting populations, and utility values; the majority of scenario analyses demonstrated similar conclusions as the base case analysis.

For these reasons, it is believed that a positive recommendation of OTL-200 would make a hugely significant contribution to MLD patients, their caregivers and families to the NHS by further enhancing the innovation of science that is critical to continue the development of future therapies and medicines.

Section A — Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SmPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

Summary:

- OTL-200 is the first technology licensed for the treatment of metachromatic leukodystrophy (MLD)
    - in children with pre-symptomatic Late Infantile (PS LI) or pre-symptomatic Early Juvenile (PS EJ) forms, without clinical manifestations of the disease.
    - in children with the early symptomatic juvenile form (ES EJ), with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.
- OTL-200 is an *ex vivo* genetically modified autologous CD34+ haematopoietic stem and progenitor cell (HSPC) gene therapy transduced *ex vivo* using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene. (Libmeldy SmPC, 2020) The lentiviral vector has been specifically designed to substantially reduce the risk of activating oncogenesis through insertional mutagenesis.
- When administered, the genetically modified cells insert one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the cell's genome, so that genetically modified cells become capable of expressing the functional ARSA enzyme. (Libmeldy SmPC, 2020)

- OTL-200 is composed of one or more infusion bags containing a dispersion of 2-10 x 10^6 cells/mL of the patient's own stem cells which have been corrected and suspended in cryopreservative solution. Each infusion bag contains 10 to 20 mL of OTL-200. Hence the treatment is highly personalised and is not batch-made. (Libmeldy SmPC, 2020)
- The safety and efficacy of OTL-200 are supported by data from a total of 35 patients: of these 29 (16 LI and 13 EJ) patients were treated with the fresh formulation (OTL-200-f) and are referred to throughout this submission as the Integrated Data Set (IDS), and six patients were treated with the cryopreserved formulation (OTL-200-c) that is the intended commercial formulation.

Figure A1: [redacted]

- Efficacy results from patients treated with OTL-200-f demonstrated that the patients who gained clinical benefit from the treatment were the PS LI and PS EJ patients and ES EJ patients treated before the onset of rapid progression of the disease. The CHMP approved indication for OTL-200 is restricted to these patients.
- This submission therefore focuses on a post-hoc analysis of efficacy data from the patients treated with OTL-200-f who fall within the anticipated market authorisation: [redacted] patients with PS LI MLD, [redacted] with PS EJ and

[redacted] with ES EJ MLD (i.e. [redacted] out of 29 patients treated with OTL-200 f); these [redacted] patients are referred to throughout this submission as the Indicated Population (IP).

- The [redacted] patients excluded from the post-hoc efficacy analysis would not meet the criteria for treatment as per the approved CHMP indication.
- Due to the short follow-up (ranging from [redacted]), efficacy and safety data available from the six subjects treated with OTL-200-c are presented separately from the data from patients treated with OTL-200-f in this document, and are included solely for the purposes of demonstrating the clear comparability of the fresh and commercial cryopreserved formulations of OTL-200.
- Preliminary safety data indicate that OTL-200 was well tolerated. The safety profile observed in the study with the cryopreserved formulation is consistent with the profile established in patients treated with the fresh formulation in terms of nature, time of onset and frequency of reported adverse events.
- After treatment with OTL-200, patients from both the clinical trial and commercial settings will be asked to enrol in a long-term follow-up study for up to 15 years in order to meet pharmacovigilance commitments and to better understand the long-term efficacy and safety of OTL-200.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with MLD	People with the following forms of MLD • Late Infantile (LI) or Early Juvenile (EJ) forms, without clinical manifestations of the disease, hereby referred to as pre-symptomatic Late Infantile (PS LI) and pre-symptomatic Early Juvenile (PS EJ) patients • EJ form with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline, hereby referred to as early-symptomatic early juvenile (ES EJ) patients	The proposed population is in line with the anticipated licensed indication shown below, for which the CHMP has granted a positive opinion OTL-200 is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of ARSA enzymatic activity: • in children with LI or EJ forms, without clinical manifestations of the disease, • in children with the EJ form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline[1] The population in the scope includes patients with Late Juvenile (LJ) and adult MLD variants who would not be eligible for treatment with OTL-200.

[1] Section 5.1 (Pharmacodynamics) of the OTL-200 SmPC defines “walking independently” as patients with GMFC-MLD score ≤ 1; and “prior to onset of cognitive decline” as patients with IQ ≥ 85. In addition, Section 4.4 (Special warnings and precautions for use), recommends treating physicians should check at both cell harvest and conditioning stage that patient is not in rapidly progressive phase of the disease.

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Intervention	OTL-200	None	N/A
Comparator(s)	Established clinical management without OTL-200, including but not limited to: • Stem cell transplant • Best supportive care	Established clinical management without OTL-200 which includes best supportive care. Stem cell transplant is not considered an appropriate comparator	Evidence from clinical experts, patient groups and the literature indicate that stem cell transplant is not used in LI or EJ MLD patients. It is only used in LJ and Adult patients who would not be eligible for treatment as per the licensed indication. As such, stem cell transplant is not included in our submission as a comparator. More details for why the stem cell transplantation is not a suitable comparator for OTL-200 are provided in Section 8.2.

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Outcomes	• The outcome measures to be considered include: • change in gross motor function • change in neurological function, for example speech and swallowing • change in neurocognitive function • change in arylsulfatase (ARSA) activity • stability of nerve conduction • age and time at severe motor impairment or death • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	None	N/A
Subgroups to be considered	If the evidence allows, the following subgroups may be considered • pre-symptomatic MLD • early-symptomatic MLD	Subgroups to be: • Pre-symptomatic Late Infantile MLD (PS LI) • Pre-symptomatic Early Juvenile MLD (PS EJ) • Early symptomatic Early Juvenile MLD (ES EJ)	

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	None	N/A
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	None	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise.	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements.	None	N/A

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Libmeldy®

Approved name: Autologous CD34⁺ cell enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene (abbreviated version: Autologous CD34⁺ cells encoding *ARSA* gene). (Libmeldy SmPC, 2020)

Therapeutic class: Libmeldy (OTL-200) is an *ex vivo* genetically modified autologous CD34⁺ haematopoietic stem and progenitor cell gene therapy. (Libmeldy SmPC, 2020)

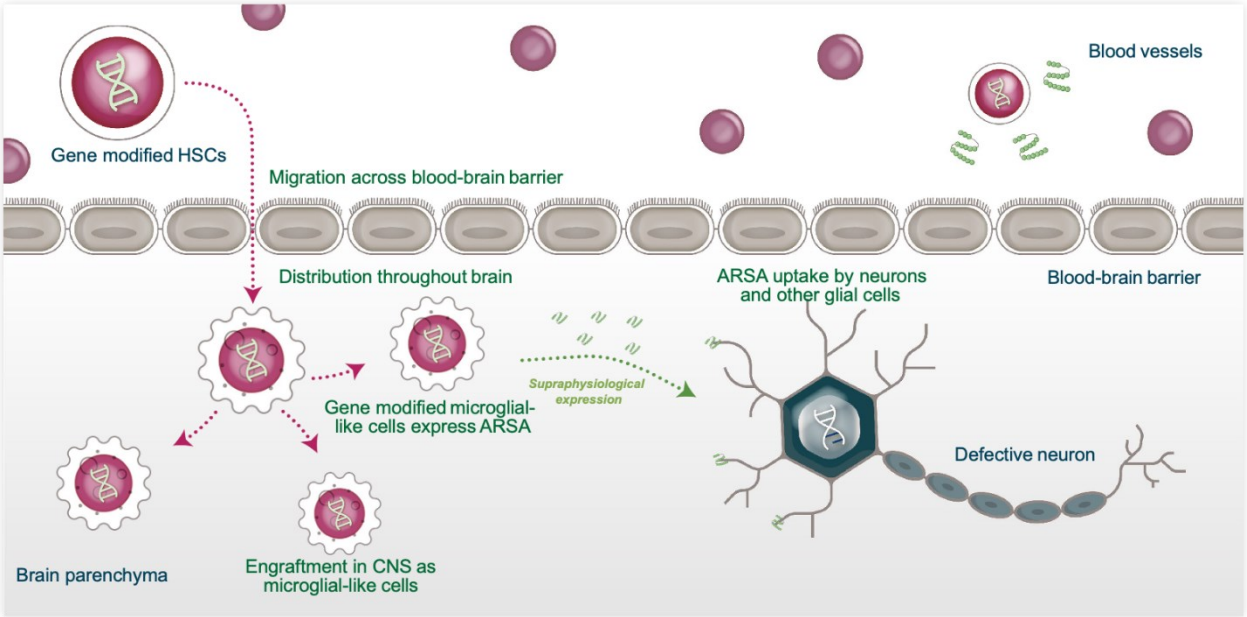
2.2 What is the principal mechanism of action of the technology?

OTL-200 is an *ex vivo* genetically modified autologous CD34⁺ haematopoietic stem and progenitor cell gene therapy. Autologous CD34⁺ haematopoietic stem and progenitor cells (HSPCs) are collected from patient bone marrow (BM) harvest or from mobilised peripheral blood (mPB) and transduced with a lentiviral vector (ARSA LVV), which inserts one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the cell's genome, so that genetically modified cells become capable of expressing the functional ARSA enzyme. (Libmeldy SmPC, 2020)

The genetically modified cells become capable of producing supra-physiological levels of the functional ARSA enzyme. When administered to the patient following the administration of a myeloablative conditioning regimen, the genetically modified cells engraft and are able to repopulate the haematopoietic compartment. A subpopulation of the infused haematopoietic stem and progenitor cells (HSPCs) and/or their myeloid progeny is able to migrate across the blood brain barrier to the brain and engraft as central nervous system (CNS) resident microglia and perivascular CNS macrophages

as well as endoneurial macrophages in the peripheral nervous system (PNS). These genetically modified cells can secrete the functional ARSA enzyme, which can be taken up by surrounding cells, a process known as cross-correction, and used to break down or prevent the build-up of harmful sulfatides (see Figure A2). (Libmeldy SmPC, 2020)

Figure A2: Illustration showing the mechanism of action of OTL-200



ARSA, arylsulfatase A; BBB, blood-brain barrier; HSC, haematopoietic stem and progenitor cell. Source: Orchard Therapeutics data on file.

Following successful and stable engraftment in the patient, the effects of the product are expected to persist throughout the patient's life. The durability of effect can be attributed to two main reasons:

(i) OTL-200 uses a retroviral vector which allows the corrected gene to be integrated directly into the genome of the target cell, where they can be replicated whenever the cell divides or differentiates. As such, the added corrected gene is subsequently passed on to all of its progeny. (Mali, 2013)

(ii) In addition, the self-renewal capability of HSPCs suggests that once the gene corrected HSPCs successfully engraft in the brain, there would be a steady supply of the genetically corrected cells and their progenies for the patient’s lifetime. (Larochelle and Dunbar, 2013, Naldini, 2019)

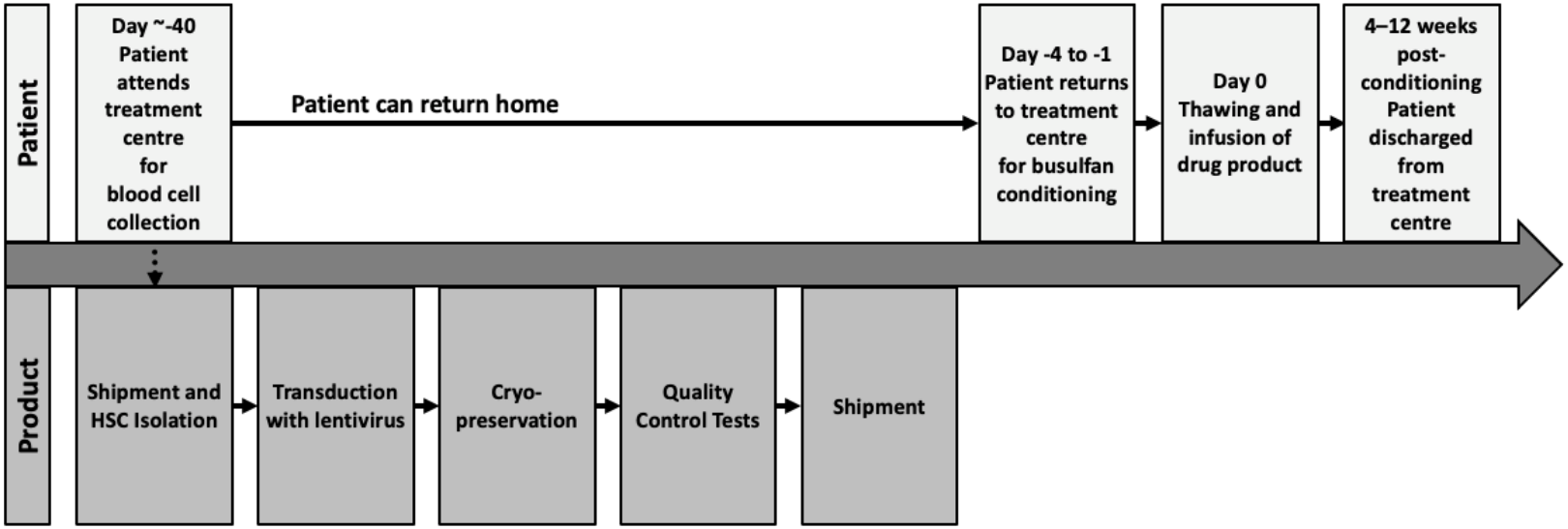
2.3 Please complete the table below.

Table A2: Dosing information for the technology being evaluated

Pharmaceutical formulation (Libmeldy SmPC, 2020)	Cryopreserved formulation. Dispersion for infusion. A clear to slightly cloudy, colourless to yellow or pink dispersion.

Method of administration (Libmeldy SmPC, 2020)	OTL-200 is administered by intravenous (IV) infusion via central venous catheter. It is intended for autologous use and should only be administered once. OTL-200 must be administered in a qualified treatment centre with experience in Haematopoietic Stem Cell Transplantation (HSCT). A myeloablative conditioning is required before infusion of OTL-200 to promote efficient engraftment of the genetically modified autologous $CD34^+$ cells. Busulfan is the recommended conditioning medicinal product. (The decision to use a myeloablative or submyeloablative regimen for pre-treatment conditioning is at the discretion of the treating physician.) Myeloablative conditioning should not begin until the complete set of infusion bag(s) constituting the dose of OTL-200 has been received and stored at the qualified treatment centre, and the availability of the back-up collection is confirmed. The decision to use BM or mPB as the source material for isolation of $CD34^+$ cells is at the discretion of the treating physician, taking into consideration the patient's age and weight, clinical condition and suitability of venous access. In general, mPB is the preferred cellular source for the manufacture of OTL-200 as it is less invasive for the patient Prior to OTL-200 infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the infusion bag(s) labels and the accompanying lot information sheet. The timing of thaw and infusion of OTL-200 should be coordinated. The infusion start time should be confirmed in advance and adjusted for thaw so that OTL-200 is available for infusion when the patient is ready. To maintain product viability, as soon as thawing is complete, it is recommended that OTL-200 be administered immediately. Administration must be completed within 2 hours from the time of thawing. Administer the product as an intravenous infusion via a central venous catheter. When more than one bag of OTL-200 is needed, only one bag of medicinal product should be infused per hour. Each bag should be infused at an infusion rate which does not exceed 5 mL/kg/h, within approximately 30 minutes. The recommended administration set consists of a blood transfusion set equipped with a 200µm filter (see section 6.6 of SmPC) It is recommended that pre-medication with intravenous chlorpheniramine (0.25 mg/kg, max. dose 10 mg), or an equivalent drug be administered 15-30 minutes before the infusion of OTL-200 to reduce the possibility of an allergic reaction to the infusion.

Doses (Libmeldy SmPC, 2020)	The dose of cryopreserved OTL-200 to be administered is defined based on the patient's weight at the time of infusion. Minimum recommended dose of OTL-200 is 3 × 10^6 $CD34^+$ cells/kg. In clinical studies, doses up to 30 × 10^6 $CD34^+$ cells/kg have been administered. The maximum volume of OTL-200 to be administered should remain < 20% of the patient's estimated plasma volume. The medicinal product is composed of one or more infusion bags containing a dispersion of 2–10 x10^6 cells/mL suspended in cryopreservative solution. Each infusion bag contains 10 to 20 mL of OTL-200. Since the total number of cells and concentration of CD34+ cells vary between individual patient batches, the quantitative information regarding strength (total viable cell concentration), volume of dispersion and total number of CD34+ cells per bag, and supplied dose of the medicinal product are provided in the Lot Information Sheet. The Lot Information Sheet is included with the cryoshipper used to transport OTL-200.
Dosing frequency	Single administration.

Average length of a course of treatment	Once eligibility of the patient has been confirmed, the treatment steps begin with cellular source harvest. After blood cells have been collected, the patient can return home while manufacturing and quality control processes take place. Once the drug product has been manufactured it is cryopreserved until the patient is ready to receive treatment. Approximately 4 days before infusion the patient returns to the treatment centre for busulfan conditioning. Patients remain at the treatment centre between 4 and 12 weeks from beginning of conditioning to discharge . Standard procedures for patient management after HSPC transplantation should be followed after the infusion. **Figure A3: Manufacture and patient treatment process for OTL-200**  (Timeline not to scale. Please note that the timings may differ slightly in clinical practice.)
Anticipated average interval between courses of treatments	None — single administration of treatment. Although the range of [redacted] days was seen in the clinical trials this would be expected to be very similar in a real world commercial setting and the median of [redacted] days would likely reduce as more clinical experience is gained.

Anticipated number of repeat courses of treatments	None — single administration of treatment.
Dose adjustments	None — single administration of treatment.

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

OTL-200 received orphan drug designation (EU/3/07/446) by the European Commission for the treatment of MLD on 13th April 2007.

It is currently being reviewed under the accelerated assessment by the European Medicines Agency (EMA). On 15 October 2020 The Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a positive opinion recommending marketing authorisation for OTL-200. The European Commission is expected to grant marketing authorisation in Q4 2020, and this will be valid in the UK.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that OTL-200 will be commercially available in the UK upon regulatory approval and the subsequent NICE appraisal process.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

OTL-200 has not received regulatory approval in any other European countries or outside of Europe.

The United States Food and Drug Administration's (FDA) has designated OTL-200 with Rare Pediatric Disease Designation for the treatment of MLD in May 2018.

3.4 If the technology has been launched in the UK provide information on the use in England.

Not applicable.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

The clinical development programme for OTL-200 (see Figure A4) comprises two clinical studies (the registrational study [Study 201222] using the fresh formulation of OTL-200 and the clinical study using the commercial cryopreserved formulation of OTL-200 [Study 205756]), and three expanded access programmes (EAPs) using the fresh formulation, including two compassionate use (CUPs) and one hospital exemption (HE) programme (Orchard Data on file, 2019a). It is anticipated that data will become available in the next 12 months from the studies as well as the EAPs. A description of all the studies for OTL-200 is summarised in Table A3, and a detailed description of each of the studies can be found in Sections 9.2–9.4.

Figure A4: [redacted]

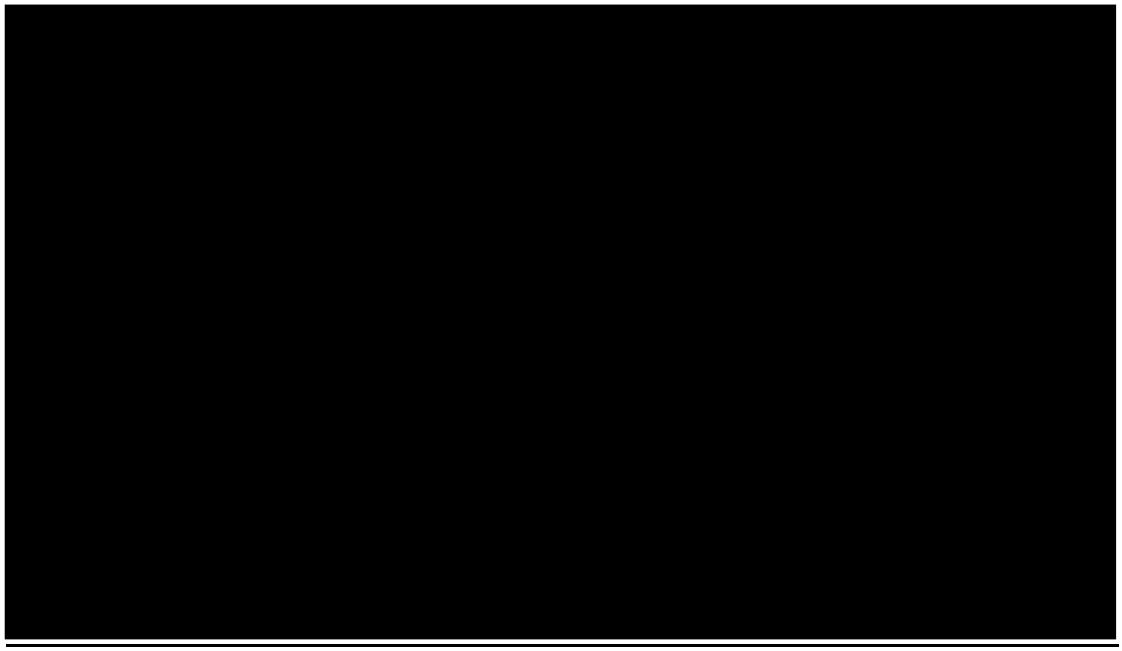


Table A3: Overview of completed and ongoing studies

Study number (Status)	Study title/Details	Patient population (Type/number of subjects)	Duration of treatment	Objectives
Phase I/II trial (Study 201222 TIGET-MLD, fresh product formulation) (enrolment closed; follow-up ongoing) (Clinicaltrials.gov NCT01560182)	Open-label, non-randomised, single-arm clinical trial evaluating the safety and efficacy of OTL-200 in patients with pre-symptomatic Late Infantile (LI) or pre- or early-symptomatic Early Juvenile (EJ) metachromatic leukodystrophy (MLD).	Patients with pre-symptomatic Late Infantile (LI) or pre- or early-symptomatic Early Juvenile (EJ) metachromatic leukodystrophy (MLD) (n=20).	Planned follow-up: at least 8 years post-treatment	To evaluate the safety and efficacy of OTL-200 in patients with pre-symptomatic Late Infantile (LI) or pre- or early-symptomatic Early Juvenile (EJ) metachromatic leukodystrophy (MLD).
EAP CUP207394 (fresh product formulation) (enrolment closed; follow-up ongoing)	One patient treated with OTL-200 in 2013.	Symptomatic EJ variant of MLD (n=1).	Follow-up ongoing	As for Study 201222.
EAP HE205029 (fresh product formulation) (enrolment closed; follow-up ongoing)	Three patients treated with OTL-200 in 2016.	Early-onset MLD patients (all pre-symptomatic LI variant) (n=3).	Follow-up ongoing	As for Study 201222.

Study number (Status)	Study title/Details	Patient population (Type/number of subjects)	Duration of treatment	Objectives
EAP CUP206258 (enrolment closed; follow-up ongoing) fresh product formulation)	Five patients treated OTL-200 in 2016.	Early-onset MLD patients (four LI, one EJ variant), all pre-symptomatic at the time of treatment (LI n=4, EJ n=1).	Follow-up ongoing	As for Study 201222.
Phase II trial (Study 205756, cryopreserved product formulation) (enrolment closed; follow-up ongoing) (ClinicalTrials.gov NCT03392987)	Open trial evaluating the efficacy and safety of the cryopreserved formulation of OTL-200 in early onset MLD patients (LI, EJ variants or intermediate variant between LI/EJ).	Ten pre- or early-symptomatic early onset MLD patients (LI, EJ variants or intermediate variant between LI/EJ).	Follow-up from end of treatment infusion until 8-year follow-up visit	To evaluate the efficacy and safety of the cryopreserved formulation of OTL-200 in pre- or early-symptomatic early onset MLD patients.
Phase III trial (cryopreserved product formulation) (currently enrolling patients — opened in June 2020) (Clinical Trials.gov NCT04283227)	Open label, non-randomized trial to evaluate the safety and efficacy of a single infusion of OTL-200 in patients with Late Juvenile (LJ) metachromatic leukodystrophy (MLD).	Up to 6 participants; if symptomatic, age at disease onset between ≥7 and <17 years of age or, if pre-symptomatic, <17 years of age at treatment with a sibling with a diagnosis of LJ MLD based on age at disease onset (≥7 and <17 years of age i.e. before sibling's 17th birthday), with biochemical and molecular diagnosis.	Planned follow-up 12 years (until January 2032).	To evaluate the efficacy and safety of the cryopreserved formulation of OTL-200 in patients with the LJ variant of MLD.

Study number (Status)	Study title/Details	Patient population (Type/number of subjects)	Duration of treatment	Objectives
Long-term follow-up study (Under discussion with EMA as part of MAA)	Long-term, efficacy and safety follow-up of MLD patients treated with ex vivo gene therapy using autologous hematopoietic stem cells transduced with ARSA lentiviral vector (OTL-200).	[redacted] patients (exact number will be known after discussions with the EMA). Patient population will comprise patients previously treated within the clinical development programme (CDP) and patients treated in the post-authorisation setting.	15 years post-treatment.	To characterise long-term efficacy and safety of OTL-200.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

The company received confirmation from the Scottish Medicines Consortium (SMC) that OTL-200 has been validated as an ultra-orphan medicine for the treatment of MLD. Based on this, a submission to the SMC is planned for 2021. The timescales for this assessment are not yet known. No other assessments are planned in the UK.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

In a recent MLD UK Health Model Advisory Board, the UK experts discussed the fact that approximately 50% of MLD patients are from a British-Asian background, and commented on the equity issues around the UK based on England, Wales and Scotland taking different treatment approaches. Another factor raised was how families with affected siblings may have greater knowledge on access to services compared to families with an index case of MLD.

The Sponsor has not identified any issues relating to equity or equality that are relevant to this evaluation, other than to reiterate that OTL-200 is a treatment for an ultra-rare and life-threatening disease for which there are no current treatment options. Therefore, a timely HST review would support NICE's commitment to promoting equality.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B — Nature of the condition

Summary

- MLD is an ultra-rare, inherited neurodegenerative disease that has a rapid and predictable course of progression. Patients experience loss of gross motor function and cognitive function resulting in extremely poor quality of life, loss of autonomy and significantly premature death. (Orchard Data on file, 2019a)
- The course of the disease is neurodegenerative, with developmental stagnation, followed by the loss of abilities in motor function, language and cognition. (Kehrer et al., 2020)
- MLD is caused by mutation in the *ARSA* gene that leads to deficient activity of ARSA enzyme. (van Rappard et al., 2015) ARSA deficiency causes accumulation of sulfatides in the nervous system leading to microglial damage, progressive demyelination and neurodegeneration. (Bergner et al., 2019, Gieselmann and Krageloh-Mann, 2010, van Rappard et al., 2016)
- The MLD disease spectrum can present in a variety of clinical forms, primarily based on the age of onset of the first symptoms of the disease. (Orchard Data on file, 2019a)
- The clinical development programme for OTL-200 focused on LI and EJ patients:
    - LI MLD (onset before age 30 months) is the most aggressive form of the disease, showing a highly predictable course characterised by a relentlessly rapid decline in motor and cognitive function within months and a significantly reduced lifespan. (Gieselmann and Krageloh-Mann, 2010, van Rappard et al., 2015) A retrospective analysis of MLD cases found that for LI patients, the 5-year survival after symptom onset was 25% and the 10-year survival was zero. (Mahmood et al., 2010)

- Patients with EJ MLD have symptom onset between the ages of 30 months and 6 years of age. EJ patients tend to have a slower and more protracted initial disease progression than LI patients. However, once symptoms occur they can progress rapidly, and once patients lose the ability to walk independently disease progression occurs at the same relentlessly rapid rate as in LI patients. For Juvenile patients (EJ and LJ combined) 5- and 10-year survival rates after onset were 70% and 44% respectively. (Mahmood et al., 2010)

- The deterioration in the physical and cognitive condition of the patient also has a significant detrimental physical, emotional, psychosocial and financial impact on carers, who are often providing round-the-clock care.
- There is currently no approved disease-modifying treatment for MLD; available treatments only treat the symptoms of the disease and none of them address the underlying cause of disease nor have proven to slow disease progression or prevent the fatal outcome.
- OTL-200 treats the underlying cause of disease by replacing the deficient ARSA enzyme. It is indicated for children with pre-symptomatic LI (PS LI) or pre-symptomatic EJ (PS EJ) MLD, without clinical manifestations of the disease, or for children with the early-symptomatic EJ (ES EJ) form who have early clinical manifestations of the disease.
- OTL-200 provides clinically meaningful benefits in the treatment of PS LI, PS EJ and ES EJ patients by preserving cognitive function, delaying time to severe motor disability and slowing down brain demyelination and atrophy. Most children treated with OTL-200 have shown normal development of motor function and cognitive skills throughout the follow-up period (of up to 8 years) to date.
- The treatment pathway (autologous use) is similar to the pathway of care already followed for HSCT in other diseases so no service redesign is required. OTL-200 has to be administered in a specialist qualified treatment centre.

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

MLD is an ultra-rare and fatal inherited genetic disorder caused by mutations in the *ARSA* gene that result in deficiency of its corresponding enzyme. ARSA deficiency causes accumulation of sulfatides in the nervous system leading to microglial damage, progressive demyelination and neurodegeneration, subsequent loss of motor and cognitive functions, and early death, especially in patients with early disease onset. (Bergner et al., 2019, Gieselmann and Krageloh-Mann, 2010, van Rappard et al., 2016)

Aetiology

MLD is an autosomal recessive inherited lysosomal disorder caused by mutations in the *ARSA* gene, resulting in a deficiency of the enzyme ARSA. (van Rappard et al., 2015)

ARSA is essential for sulfatide metabolism through the hydrolysis of the 3-O ester bond of galactosyl and lactosyl sulfatides. Its deficiency results in accumulation of sulfated glycolipids, in particular, cerebroside sulfate or galactosylceramide-3-O-sulfate (sulfatide) in the myelin sheaths of the nervous system, and to a lesser extent in visceral organs like liver, gallbladder, kidney, lymph nodes, adrenal glands and ovaries.

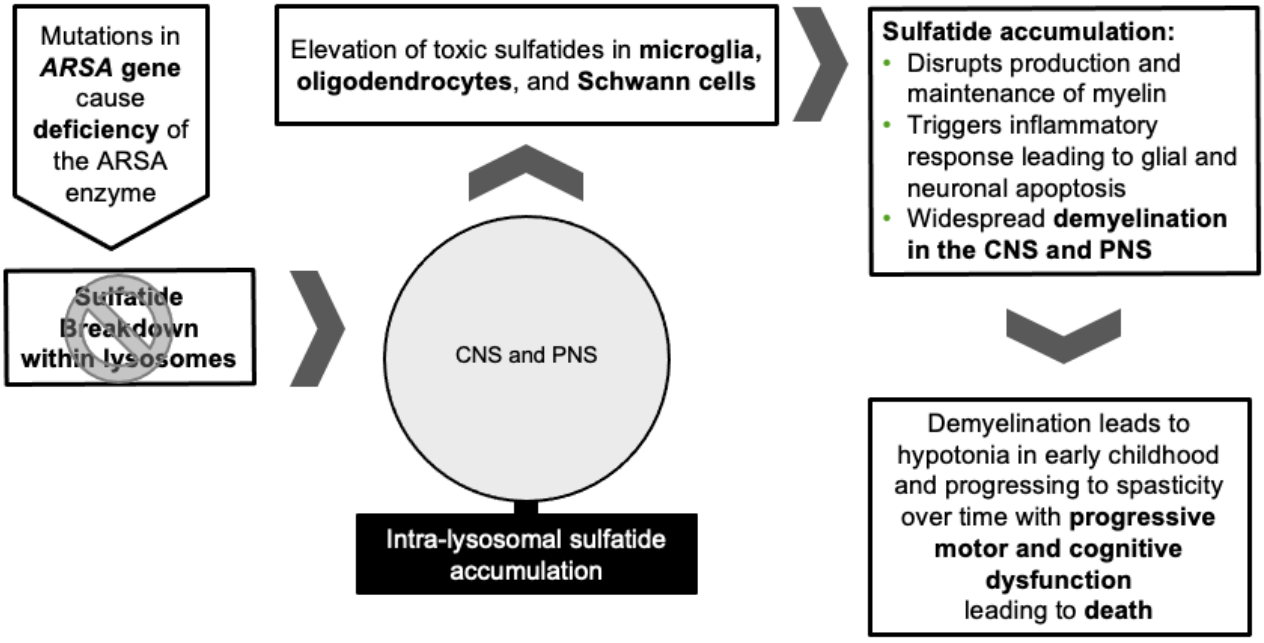
Sulfatides accumulate in the oligodendrocytes, macrophages and some subtypes of neurons in the central nervous system (CNS), and in Schwann cells and macrophages of the peripheral nervous system (PNS). The excess of sulfatides can lead to abnormal myelin composition and possibly affect the formation of a stable lipid bilayer.

With the progressive accumulation of sulfatides, the lysosomal-endosomal system becomes dysfunctional, and other secondary pathogenic cascades

occur, ultimately resulting in cell death. This results in progressive demyelination in both CNS and PNS, which correlates with the major clinical manifestations of MLD.

The complexity of the neurodegenerative process is not well understood. In addition to myelin sheaths, neurons are also affected in MLD. This may explain why neurological symptoms and neuroradiological evidence of demyelination do not always progress in parallel (Kohlschutter, 2013).

Figure B1: Pathophysiology of MLD



Adapted from the following sources: (Rosenberg et al., 2016, Patil and Maegawa, 2013, Stein et al., 2015, NIH, 2019)

Mutations in the *ARSA* gene can be functionally divided into two groups (Wang et al., 2011, Gomez-Ospina, 2006):

- Null alleles (0-type alleles), which result in the complete loss of enzymatic activity.
- Non-null alleles (R-type alleles), which encode for ARSA with residual activity.

Individuals who receive a copy of the pathogenic mutated *ARSA* gene from both parents will suffer from some variant of MLD.

Natural history

The clinical course of MLD can be broadly divided into a pre-symptomatic stage with normal motor and cognitive development, followed by a period of developmental plateau and early onset of first symptoms (early symptomatic), which is short in early-onset forms and longer and more variable in late-onset forms.

The disease inevitably ends in a decerebrated state and eventually premature death for all phenotypic forms of the disease, although its course and duration are variable. (Biffi et al., 2008, Elgun et al., 2019, van Rappard et al., 2015)

There is no universally accepted classification system for MLD phenotypes, however historically MLD has been classified into Late Infantile (LI), Juvenile, and Adult phenotypes (see Figure B2). The classification is based on age of onset of the first symptoms of the disease (Kolodny, 1995, von Figura et al., 2001). The juvenile forms are further classified into Early Juvenile (EJ) and Late Juvenile (LJ) phenotypes (variants). (Kehrer et al., 2020) Despite this standard classification into different clinical phenotypes, it is well known that the underlying disease pathophysiology is common for all phenotypic forms of MLD. (Biffi et al., 2008) The LI and EJ variants are collectively referred to as early-onset MLD, while LJ and Adult variants are referred to as late-onset MLD. The rest of this section will focus on LI and EJ MLD, given this is the population containing the patients who would be eligible for OTL-200 as per the CHMP approved indication (PS LI, PS EJ and ES EJ patients).

Figure B2: MLD spectrum and evolving classification

	LATE INFANTILE (LI)	JUVENILE		ADULT (AD)
		EARLY JUVENILE (EJ)	LATE JUVENILE (LJ)	
ARSA activity				
Age at onset	< 30 months	30 months – 6 years	7 – 16 years	17 years and over
Median survival	2.7 years (post onset)	9 years (post onset)		25 years (post onset)
Initial symptoms	• Gait abnormality • Abnormal movement patterns • Weakness, Hypotonia • Clumsiness, frequent falls	Same as LI plus; • Fine – Motor – Function • Aggression, Irritation • Concentration	• Inattention • Poor school performance • Prominent behavioural abnormalities	• Intellectual defects • Memory defects • Emotional & behavioural problems
Dominant trigger	**MOTOR** Missing milestones Developmental Regression Motor and language skills	**MOTOR +/- COGNITIVE**	**COGNITIVE** Cognitive decline School performance Behavioural change Educational problems	**NEURO-PSYCHIATRIC** Personality changes Decline mental functions Psychotic disturbances Loss of coordination/spasticity

LI variant:

- Patients who are clinically classified with the LI variant usually carry two null alleles (0/0 genotype) and express no residual ARSA activity (Wang et al., 2011), resulting in manifestation of symptoms before 30 months of age. (Gieselmann and Krageloh-Mann, 2010, van Rappard et al., 2015, Wang et al., 2011)
- LI MLD is the most aggressive form of the disease showing a highly predictable and severe disease course, characterised by a rapid progressive decline in motor and cognitive function and an early death (Gieselmann and Krageloh-Mann, 2010, van Rappard et al., 2015); a retrospective analysis of MLD cases since 1921 showed that the 5 -year survival after onset of symptoms was 25% and the 10-year survival was zero (Mahmood et al., 2010).
- LI MLD is the most common variant: European studies suggest that approximately 40% to 60% of MLD patients have the LI variant. (Gieselmann and Krageloh-Mann, 2010, Gomez-Ospina, 2006, Heim et al., 1997, Lugowska et al., 2005, Poorthuis et al., 1999)

EJ variant:

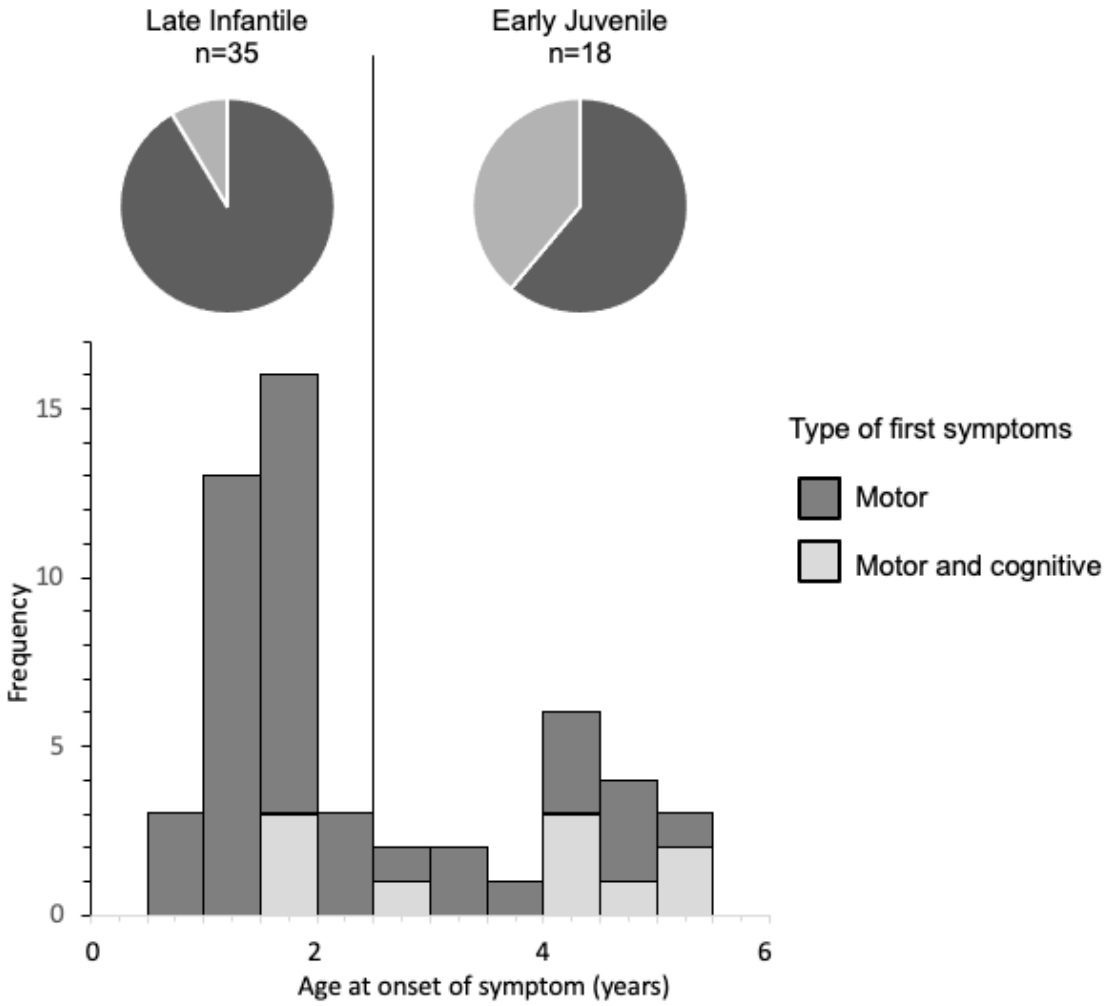
- Patients with the EJ variant carry either one null allele and one residual allele (0/R genotype) or (less frequently) two residual alleles (R/R genotype); these patients have symptom onset between the ages of 30 months and 6 years of age (before their 7th birthday), and tend to have a slower and more variable initial disease progression than LI patients. However, once symptoms occur, they can progress rapidly and once patients lose the ability to walk independently disease progression occurs at the same rate as in LI patients.
- A retrospective analysis of MLD cases since 1921 showed that, for juvenile patients* (EJ and LJ together; mean age of diagnosis 10 years), 5- and 10-year survival rates after symptom onset were 70% and 44%, respectively. (Mahmood et al., 2010)
- European studies suggest that approximately 20% to 40% of patients have the juvenile variant* (EJ or LJ). (Gieselmann and Krageloh-Mann, 2010, Gomez-Ospina, 2006, Heim et al., 1997, Lugowska et al., 2005, Poorthuis et al., 1999)

Clinical manifestations

The clinical presentation of MLD varies with respect to age of onset and speed of disease progression (Beerepoot et al., 2019).

* Although the Juvenile variant is often subdivided further into EJ and LJ, with an onset of symptoms before or after the age of 6 years, most publications on natural history of disease present aggregated data for juvenile patients making it difficult to report the natural course of EJ disease on its own. However emerging evidence has shown that LJ patients generally have a more protracted course of disease compared to EJ patients. (Kehrer et al. 2020)

Figure B3: Distribution of type and age of first symptoms in LI and EJ MLD patients



Source: (Kehrer et al., 2020)

Forty-six percent of patients with LI MLD (onset before age 2.5 years) develop their first motor symptoms (such as gross motor delay, abnormal movement patterns and motor regression) before the age of 18 months. (Kehrer et al., 2020)

LI patients lose the ability to walk without support (GMFC-MLD Level 2) at a mean of 0.43 years after the onset of disease, and locomotion and the ability to sit without support (GMFC-MLD Level 5) at a mean of 1.15 years from disease onset. (Kehrer et al., 2020)

As the disease progresses, language and cognitive skills regress. (Gomez-Ospina, 2006) Language decline occurs at a mean age of 30 months with

complete loss at a median age of 32 months (Kehrer et al., 2014) The ability to communicate in any form is lost at just over 4 years of age. (Kehrer et al., 2014) Spastic tetraparesis and other CNS manifestations develop. (Beerepoot et al., 2019) PNS symptoms frequently observed in later stages of early onset MLD are: neurogenic bladder dysfunction, presenting with unexplained signs of discomfort, frequency or retention and sometimes needing intermittent catheterisation; neuropathic pain; and severe foot deformities. (Beerepoot et al., 2019) In the final stages, children have tonic spasms, decerebrate posturing, and general unawareness of their surroundings. (Gomez-Ospina, 2006)

EJ MLD usually present with either motor symptoms alone (~60%) or a combination of motor and cognitive symptoms (~40%) (Kehrer et al., 2020).

In EJ patients, gross motor function deteriorates as the disease progresses, although the initial rate of decline can be variable (Kehrer et al., 2011a). Initial difficulties in performing activities such as running are followed by problems with walking and standing, resulting eventually in a complete loss of walking ability. (Harrington et al., 2019) Once symptoms occur they can progress rapidly, and once patients lose the ability to walk independently disease progression occurs at the same rate as in LI patients.

As with LI patients, individuals eventually progress to swallowing difficulties requiring the placing of a gastrostomy tube and breathing difficulties (Harrington et al., 2019)

Decline in cognition begins with problems in concentration, followed by a decline in reading, writing and calculating skills. (Kehrer et al., 2014) Parents report concentration issues and disruptive behaviour, (Harrington et al., 2019) followed by language decline leading eventually to a complete loss of language and subsequent loss of ability to communicate in any form. (Kehrer et al., 2014)

Table B1 provides an overview of the time from disease onset to clinical presentation of motor and cognitive symptoms for LI and EJ patients.

Table B1: Time from disease onset to clinical presentation of motor and cognitive symptoms in years for LI and EJ patients

Clinical endpoints		LI MLD	EJ MLD
GMFC-MLD Level 2	Mean ±SD 95 % CI	0.43±0.09 0.26 – 0.60	1.63±0.32 1.00 – 2.25
GMFC-MLD Level 5	Mean ±SD 95 % CI	1.15±0.12 0.93 – 1.38	2.47±0.50 1.49 – 3.46
Swallowing difficulties	Mean ±SD 95 % CI	1.15±0.12 0.92 – 1.38	2.12±0.50 1.19 – 3.14
Tube feeding	Mean ±SD 95 % CI	3.19±0.69 1.84 – 4.54	3.50±0.74 2.05 – 4.94
Language decline	Mean ±SD 95 % CI	0.87±0.10 0.68 – 1.06	1.37±0.35 0.68 – 2.06
Loss of expressive language	Mean ±SD 95 % CI	1.63±0.35 0.95 – 2.30	2.54±0.45 1.65 – 3.43

Source: (Kehrer et al., 2020)

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

Prevalence

There is no officially-recognised registry of MLD patients although Orphanet, the portal for rare diseases and orphan drugs, reports the worldwide prevalence of MLD as 0.1–0.9 per 100,000. (Orphanet, 2019). Also, a recent population-based, UK-wide study of physician-reported progressive intellectual and neurological deterioration (PIND) in children between 1997 and 2014 identified 76 children with MLD of which 57 were LI and 10 EJ (Stellitano et al., 2016). The majority of these would have already died.

According to communication from PAGs and clinical experts (NICE scoping meeting on Jan 27th 2020 meeting and Orchard Therapeutics clinical advisory boards — Completed on 10th Oct 2019 and 21st Oct 2020)., there are currently 29 known MLD patients in the UK (13 LI, six EJ and 10 Adult), giving a prevalence of approximately 0.04 in 100,000 but very few of these would be

eligible for treatment given the indication of OTL-200 is restricted to pre-symptomatic LI and EJ patients as well as early symptomatic EJ patients only.

Incidence

The birth prevalence of MLD has been estimated as 6.8 per million live births in the UK (Stellitano et al. 2016). Based on 640,370 live births in England and Wales in 2019 (ONS 2019), about 4–5 MLD patients would be born every year, of which about [redacted] patients would be expected to have the indicated LI or EJ variants.

Expert opinion from clinicians at the three specialist clinical centres where MLD is currently managed and diagnostic laboratories estimate that a maximum of [redacted] LI PS patients and [redacted] EJ ES patient would be eligible for OTL-200 treatment every year given the proposed indication (Communication from Clinical Experts and Patient Advisory Groups shared at NICE scoping meeting 27th January 2020 — Orchard Therapeutics Clinical Advisory Boards — Completed on 10th Oct 2019 and 21st Oct 2020).

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

Currently we are not aware of any published MLD survival data for England alone.

A retrospective analysis of MLD cases worldwide since 1921 (Mahmood et al., 2010) found that for LI patients, the 5-year survival after onset of symptoms was 25% and the 10-year survival was zero (although since 1970 increased survival rates in an advanced decerebrated stage of the disease have been observed, likely due to improvements in supportive palliative care). For juvenile patients (mean age of diagnosis: 10 years), 5- and 10-year survival rates were 70% and 44%, respectively.

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

The burden of MLD for children, caregivers and their families has been illustrated in three recently conducted independent studies. These three studies are presented in Section 7.1 to describe the impact MLD has on the quality of life of patients, their families and caregivers, including the impact of the condition on physical health, emotional wellbeing and everyday life.

The MLD caregiver study (Pang et al., 2020) was designed to comprehensively qualitatively and quantitatively assess the burden of MLD based on a survey of 21 caregivers across a range of domains, including personal and family relationships, personal time, daily activities, physical and mental health, social life, leisure activities, work productivity, and finances. (Pang et al., 2020) The study was based on a moderator guided survey and follow-up extended semi-structured telephone interviews with caregivers from the UK (n=6), Germany (7) and the US (n=8). The questionnaires were extensively validated with clinical KOLs and representatives of patient organisations and submitted for IRB approval. Careful consideration was given to the study design due to the challenges in recruitment because of MLD as an ultra-rare disease and the methodological issues associated with proxy administration (which are not limited to this particular study). The MLD caregiver study took over 20 months from design, validation, IRB approval, recruitment through to analysis.

Similar findings were reported in another caregiver study (Harrington et al., 2019) assessing the burden affecting MLD caregivers as part of their attempt to develop and validate an instrument measuring the impact on caregivers of caring for children with three lysosomal storage diseases (LSDs): metachromatic leukodystrophy (MLD), neuronopathic mucopolysaccharidosis

type II (MPS II) and mucopolysaccharidosis type IIIA (MPS IIIA). (Harrington et al., 2019)

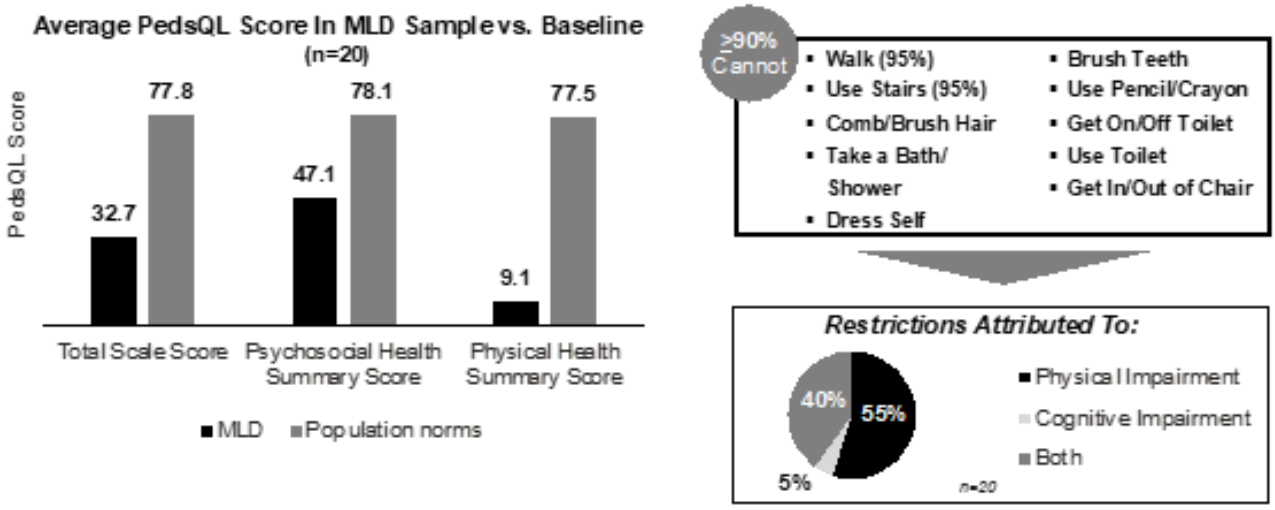
A third caregiver study (Eichler et al., 2016) was conducted to capture the caregiver perspectives to identify relevant clinical/quality-of-life domains for patients and caregivers, also as a precursor for the development of a conceptual model for a *de novo* patient-reported outcome measure. Interviews and one focus group were conducted with 30 caregivers representing 23 patients. Caregivers were asked about their experiences, including diagnostic process, signs/symptoms, symptoms affecting caregivers' and patients' lives, and treatment priorities.

Impact on quality of life of patients

The impairments experienced by patients with MLD in functional (motor) and cognitive ability can have a substantial burden on the quality of life of patients. The progressive impairment of mobility/functional capacity, results in wheelchair dependence or severe immobility, substantially impacting the independence of the patient and making it difficult for patients to complete activities of daily living. The majority of affected MLD children lose their motor and cognitive function within 3 years of disease onset and become bedridden with severe cognitive impairment. (Kehrer et al., 2020) This has been reflected through the implementation of quality of life questionnaires, which indicate scores below population norms. The MLD caregiver study (Pang et al., 2020) measured the quality of life of patients (n=20) with MLD (Late Infantile and Juvenile) using the well-validated PedsQL instrument for children and adolescents and determined the average PedsQL total score to be 32.7 (out of a total of 100) which is significantly less than the average score of 77.8 for the general population (Figure B4). The UK caregivers (n=6) reported a 3.7 out of 100 PedsQL physical score compared to an average score of 85 for the general population and 39.3 out of 100 PedsQL psychosocial score compared to an average score of 90 for the general population. (Pang et al., 2020)

Cognitive impairment can also impact the independence and confidence of patients and affect many aspects of social functioning; patients with MLD will require extra education/special schooling and are unlikely to ever obtain full-time employment. In the MLD caregiver survey, 25% of children were not attending school or receiving home schooling. (Pang et al., 2020) Of those attending school, over 50% often or almost always experienced problems, especially keeping up with activities, forgetting things, and paying attention in class as measured by the school functioning domain of the PedsQL. (Pang et al., 2020)

Figure B4: Caregiver reported impact on quality of life and physical functioning



Note: Values for population norms were from US, Germany and UK (Varni et al., 2001, Listing et al., 2018, Upton et al., 2005). The PedsQL was completed by 20 out of 21 caregivers
Source: (Pang et al., 2020)

Only 35% of caregivers reported their child's quality of life as good or very good within the past month. Over 90% of caregivers reported that their child could not walk, use stairs, dress themselves, use the toilet independently or brush their teeth. These limitations in basic activities of daily living were attributed to the patients having significant physical impairment (55%), cognitive impairments (5%) or a combination of both (40%). (Pang et al., 2020)

Impact of quality of life of caregivers and families

As with other chronic conditions, the impact of MLD on caregivers/family is greatly underestimated. The burden of caring for patients with MLD is largely attributed to the appropriate management of the patient's daily life. For patients with MLD, most become wheelchair dependent or severely immobile and patients never achieve social independence. MLD patients are consequently highly reliant on third-party assistance with cognitive impairment, reduced self-care and reduced locomotive abilities as the key reasons behind this dependency.

Impact on emotional, social and psychological wellbeing

In the MLD caregiver study (Pang et al., 2020), (respondents (n=21) reported often being forced to make sacrifices in the social lives and personal lives with 95% of the caregivers reporting needing to make significant lifestyle changes due to their caregiving duties. In addition, 52% of caregivers reported being overwhelmed and 48% felt impaired due to being worried about the future. Caregivers attributed these negative emotions to a loss of identity, poor self-care and feeling unable to help their child. (Pang et al., 2020)

The burden of caregiving is usually the responsibility of the parent. However, the wider family and unaffected siblings of patients with MLD often provide a supportive caregiver role, which may impact their life decisions and ability to work. This suggests that the effects of MLD on QoL can extend beyond the parents to all members of the family, such as to limit the educational potential and reduce the quality of life of siblings. In terms of familial dynamics, there was a significant or extremely negative impact of MLD in 52% of caregivers with their spouse/partner, 29% with other family members, 24% with other children, 19% between siblings and 10% with the affected child itself. (Pang et al., 2020)

95% of caregivers had to make significant lifestyle changes and 71% indicated that they missed leisure activities they once enjoyed. (Pang et al., 2020)

Similarly, in the caregiver study (Harrington et al., 2019), all caregivers reported an impact on their ability to participate in social activities (16/16;

100%), over half of the MLD caregivers (9/16; 56%) reported a negative impact on their spousal relationship or time available to spend with their spouse, and most felt they could not give their other family members as much attention as they would like (15/16; 94%). All caregivers (16/16; 100%) also described how their emotions had changed from the time of their child's diagnosis to the present time, with some describing going through a grieving process, as though they had already lost their child. (Harrington et al., 2019)

In the caregiver study (Eichler et al., 2016) of 30 caregivers representing 23 MLD patients (Eichler et al., 2016), caregivers reported that the time and attention spent caring for their family member confined members of the family to the home (16/30), leading to feelings of depression (8/30), worry (8/30) and sadness (8/30), feeling of fear (11/30), and guilt, remorse and hopelessness. Caregivers also reported that the disease had an impact on the patient's siblings as they struggled to understand the disease (7/30).

Impact on caregiver physical health

Caregivers (typically parents) of patients with MLD experience a reduced quality of life, which worsens over time. Daily caregiver activities include providing general health maintenance (e.g. bathing and cleaning up), provision of therapy, moving and lifting patients, monitoring patients' vitals, feeding and suctioning of extra saliva. These activities all contribute to caregivers having significant physical health challenges. Carers are required to take time off work and may experience anxiety and depression. They may also be at risk of injury (e.g. back injuries) due to handling/moving patients. (Eichler et al., 2016)

To capture the direct health impact on caregiver health and physical functioning, the EQ-5D-5L was administered to caregivers (n=21) in the MLD caregiver study. (Pang et al., 2020) Seventy-one percent of all respondents (15/21) reported experiencing moderate to severe anxiety/depression and 62% of respondents (13/21) experienced moderate to severe pain/discomfort. The UK caregivers (n=6) reported that 83% (5/6) experienced moderate to severe anxiety/depression and 66% (4/6) reported experienced moderate to severe pain/discomfort. The mean EQ-5D index values reported by the

caregivers (n=21) was lower than that of the population norms in their respective country of residence, particularly in the UK the caregivers (n=6) reported an overall VAS mean of 70.5 with a population norm of 77.2. (Pang et al., 2020)

Figure B5: UK caregiver self-reported EQ-5D-5L scores and mean EQ-5D VAS

UK Caregiver Self-Reported EQ-5D-5L Scores (n=6)

	MOBILITY	SELF-CARE	USUAL ACTIVITIES	PAIN/ DISCOMFORT	ANXIETY/ DEPRESSION
Any Problems	**17%**	**17%**	**34%**	**66%**	**83%**
Population Norm[1]	18.4%	4.3%	16.3%	33%	21%

UK Mean EQ-5D Index Values Compared to Population Norms by Country (n=6)

Note: Table represents Caregiver reported EQ-5D Index Values conducted in the 5L format and cross-walked to compare to 3L population norms EQ-5D-5L crosswalk values generated through EQ-5D-5L Crosswalk Index Value Calculator. Population norms obtained from Table 3.5 of "Self-Reported Population Health: An International Perspective based on EQ-5D"
Source: (Pang et al., 2020, van Hout et al., 2012, Szende et al., 2014)

Impact on caregiver time

Parents are usually the main provider of care, with one parent often becoming a full-time carer, providing round-the-clock care. Due to the amount of effort required to care for a patient with MLD, there is also potential for sibling abandonment, which may impact on the development of the unaffected sibling. In the MLD caregiver study (Pang et al., 2020), caregivers (n=21) reported that on average over the past year they spent 17 hours per day providing care to the children. This included general health maintenance (e.g. bathing, brushing team, changing nappies, emptying catheter), moving or lifting (e.g. in/out of bed, bathroom, vehicle), monitoring and checking vitals (e.g. blood pressure, temperature, oxygen), feeding (with or without tube), medication administration (at multi-hour intervals, sometimes administered in the middle of the night), organising therapies (e.g. physical, occupational,

speech, music). The UK caregivers (n=6) reported that they spend on average 15 hours per day caring for their child. In addition, on average for each affected child, 3 caregivers (parents and nurse assistant) made up the care team. Others drafted into the care team included grandparents, siblings, uncles and aunts. Half of the caregivers (n=11) received on average over the past year 6 hours per day of nursing care. Due to the round the clock care required, a caregiver indicated even going grocery shopping was a difficult undertaking. (Pang et al., 2020)

Impact on caregiver ability to work

Caregivers of patients with MLD may be unable to work full time, although this depends on the severity of the disease; caregivers of wheelchair-bound or severely-immobile patients are unlikely to be able to work. Caregivers normally have to limit their careers to jobs that are less demanding, which typically provide lower salaries or give up work entirely. In the MLD caregiver study (Pang et al., 2020), caregivers (n=21) described the financial impact of caring for a child with MLD disease, which included giving up work to care or being unable to return to work, having time off from work, additional expenses, benefits and waiting for funding. 83% of the caregivers were forced to miss work with an average of 68% of the time being unpaid; 65% experienced loss of income due to stopping work or moving to part-time. (Pang et al., 2020)

Impact on caregiver out of pocket expenses

Caring for a patient with MLD generally results in additional out-of-pocket expenses. Examples include non-reimbursable expenses due to travel, additional costs for vacations/excursions, and supportive services. Families can receive financial assistance for certain elements of care, such as financial aid for wheelchairs and home adaptations; however, home adaptations are means-tested, therefore not all families will receive support. While 57% of respondents had to depend on external sources of funding to help with management of the patient’s disease, the caregivers from the UK (n=6) reported that 84% of the national annual median income per capita is consumed by out-of-pocket expenses and forgone income (Pang et al., 2020)

Similarly, in the caregiver study (Harrington et al., 2019) findings were reported that caregivers experience financial strain because of their child's illness (13/16; 81%), and half (8/16; 50%) reported being unable to work because of caregiving responsibilities. A similar pattern of saturation was evident for caregivers of children with MLD from the Late Infantile and juvenile onset groups.

Personal communications from a patient group have indicated this financial burden of MLD can be severe with families reporting financial impact of more than £260,000 to cover purchasing of essential home equipment, community services, lost earnings and respite costs.

Coming to terms with the new normal	"My biggest fear was losing who she was. We are grieving and we were grieving for the last nine years. It's an ongoing process, it never goes away. You see, any situation becomes the new normal, but it's a constant sadness that we deal with. It's not going to get better, but you've learned to live with it." – Caregiver (UK)
Communication with child	"I think the biggest challenge as a parent was seeing the frustration in my daughter's eyes. I don't think the kiddos get enough credit for how much they know and understand especially at a young age. … It has been very apparent to me that she knows what's going on, and as she has lost her abilities you could see the frustration in her face and how upset it would make her." - Caregiver (US)
Managing feelings of grief	"We've grieved what we lose and then you grieve again when the time comes, the whole 9 years we've been grieving, it becomes the new normal, it's not going to get better, but you learn to live with it." – Caregiver UK
Physical decline	"I suppose at the point [child's name] is now where she's on palliative care and she can't really do anything, there's nothing else. We don't really see a physio anymore because they feel like there's not much point because we're not working towards something." – Caregiver (UK)

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Overall, OTL-200 is expected to have a profound impact on patients, their families and caregivers because OTL-200 is a step-change in the management of patients with MLD. Based on the experience with the technology throughout follow-up of up to 8 years, quality of life for patients is expected to improve following the one-time treatment

As demonstrated in the overview of clinical studies presented in Section C, OTL-200 provides meaningful clinical benefits in the treatment of children with PS LI, PS EJ and ES EJ by preserving cognitive function, delaying time to severe motor disability and slowing down brain demyelination and atrophy. Children treated with OTL-200 are anticipated to show normal development of motor function and cognitive skills, sustaining the time during which they are comfortable and alert and allowing them to develop and maintain daily activities of living, such as walking and self-feeding, as well as build normal relationships with family members and caregivers. These qualitative outcomes are consistent with the totality of evidence of long-term clinical benefit.

These clinical benefits are expected to translate into longer life expectancy for MLD patients. Earlier treatment of pre-symptomatic patients is expected to lead to greater outcomes as disease progression may be halted and patients will never show the classic manifestation of disease, thus developing similarly to other children, gaining development milestones (and restoration to normal population health).

In addition to providing direct clinical benefits to the patient, OTL-200 is anticipated to have a significant impact on the daily lives of the family and caregivers by improving quality of life, wellbeing and reducing time spent caring. A reduction in the length and intensity of caring may also reduce the

risk of mental health problems and familial dynamics. The effects of OTL-200 into adulthood have not been studied as all patients treated with OTL-200 are still minors, but it is expected that children who are able to attend school will become adults who are able to work and contribute to society.

Therefore, OTL-200 will positively impact several key factors of family life including:

- The emotional, social and psychological well-being of caregivers and their families
- The ability to build and sustain normal relationships with family, friends and social relationships
- The education and social interaction of the affected children who have a chance to grow up and lead normal lives
- Work productivity gains for parents/caregivers and the ability to pursue career ambitions
- Family finances and outside sources of financial support, including friends

These cost savings have not been included in the cost-effectiveness and budget impact model, since it is not possible to provide estimates at this time. Therefore, the presented cost-effectiveness and budget impact figures for OTL-200 in Section D are conservative estimates.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

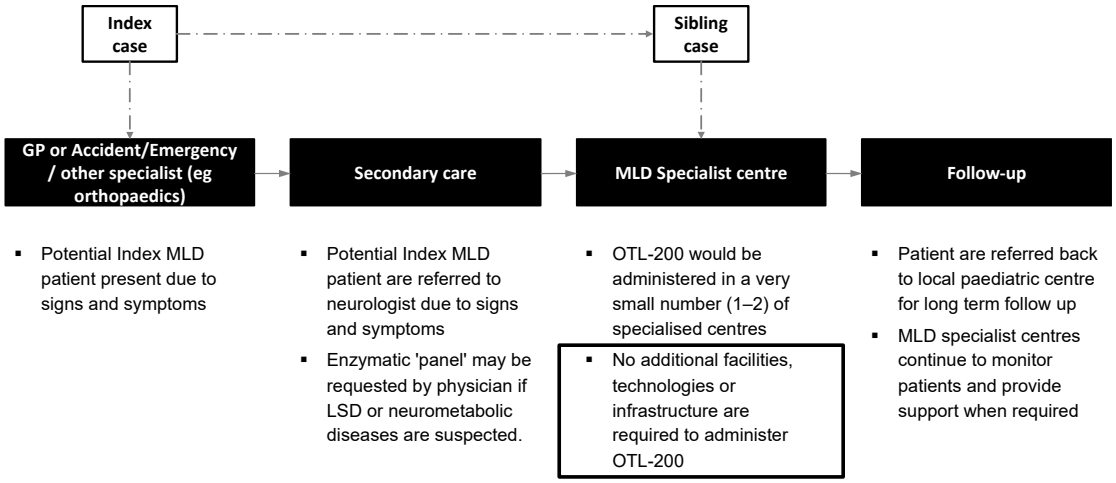
There are currently no NICE, NHS England or other national guidelines for the treatment and management of MLD.

The Global Leukodystrophy Initiative (GLIA) consortium[2] have published guidelines on the preventive and symptomatic care of patients with leukodystrophies (including MLD) (Adang et al., 2017, Van Haren et al., 2015). As these guidelines are for all leukodystrophies, they do not identify subgroups of MLD or make specific recommendations for their treatment. Details of the guidelines are summarised in Appendix A.

[2] The Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN) is a consortium of scientists, industry stakeholders, and patient advocacy leaders working together to promote advances in the diagnosis and treatment of leukodystrophies. GLIA-CTN work closely with a diverse group of stakeholders to promote disease awareness and education, advocate for the adoption of universal newborn screening and early diagnostic programs, and establish clinical guidelines to support the short- and long-term care of individuals living with leukodystrophies

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Figure B6: MLD clinical pathway of care



In England, MLD patients are managed by local paediatric specialists who refer the patients to one of the three paediatric lysosomal storage disease (LSD) specialist centres[3] for expert treatment by a multi-disciplinary team led by paediatric metabolic consultant. An overview of the clinical pathway of care for MLD patients is presented in Figure B6 and a description of the various steps is described below.

The SmPC for OTL-200 requires treatment to be administered at a qualified specialist treatment centre with experience in delivering HSCT for neurometabolic patients. The company is in discussions with NHS England regarding the qualification of one of the three paediatric LSD specialist centres for administration of OTL-200. As all three centres have experience in delivering allogeneic HSCT for other neurometabolic diseases, changes to the existing clinical care pathway are expected to be minimal and will not involve significant alteration to the current service provision by NHS England, especially as the expected patient population to be treated is approx. [redacted] over the coming years.

[3] The three UK Lysosomal Storage Diseases (LSD) Specialist Paediatric Centres in England are Great Ormond Street Hospital, London; Birmingham Children's Hospital; and St Mary's Hospital, Manchester.

Diagnosis and assessment

Currently diagnosis is largely symptom-led, however if newborn screening were to be introduced then more patients would be diagnosed at a pre-symptomatic stage but this is currently significant years away from realisation as it can take in excess of 10 years or more. Currently, some patients are diagnosed pre-symptomatically following screening as a result of an older sibling being diagnosed with MLD.

MLD is suspected in individuals with the following:

- **Progressive neurologic dysfunction:** Presenting signs may be motor and/or behavioural/cognitive. Progression is determined both by history and by physical examination. (Gomez-Ospina, 2006) Family history of neurological disease, time of onset of neurological symptoms, the presence of gait abnormalities, spasticity, decreased muscle stretch reflexes are also important considerations. (Kohlschutter, 2013, McKhann, 1984)
- **Magnetic resonance imaging (MRI) evidence of demyelination:** Diffuse symmetric abnormalities of periventricular myelin with hyper-intensities on T-weighted images. Initial posterior involvement is observed in most Late Infantile cases with subcortical U-fibres and cerebellar white matter spared. As the disease progresses, MRI abnormalities become more pronounced in a rostral-to-caudal progression; cerebral atrophy develops. Anterior lesions may be more common initially in individuals with later onset. (Kohlschutter, 2013, Gomez-Ospina, 2006) In early stages of the disease, a normal MRI may not rule out a diagnosis of MLD, as the demyelination changes may be subtle.

If MLD is suspected, diagnosis is based upon combination of biochemical procedures and genetic analysis. (van Rappard et al., 2015)

- **ARSA activity:** On clinical suspicion of MLD, ARSA enzyme activity is usually measured in isolated blood leukocytes. The diagnosis of MLD is suggested by ARSA enzyme activity in leukocytes that is less than normal controls using the usual synthetic substrate-based assay. (Gomez-Ospina, 2006)
- **Molecular analysis:** Because low ARSA activity can occur in healthy individuals — pseudodeficiency (PD) mutation occurs at an estimated rate of 5-20% (Gomez-Ospina, 2006) — the diagnosis of MLD can also be confirmed by molecular genetic analysis of the ARSA gene. This testing is used for confirmatory diagnostic testing to determine if low ARSA enzyme activity results from either of the following (Wang et al., 2011, Gomez-Ospina, 2006):
    - Homozygosity or compound heterozygosity for an ARSA-MLD variant(s).
    - A combination of known non-disease-causing alleles such as ARSA-PD homozygosity or compound heterozygosity for an ARSA-MLD and an ARSA-PD variant, which suggest the carrier state for MLD.
- **Urinary sulfatides:** In MLD patients, sulfatides accumulate in the urine in amounts from 10- to 100-fold higher than in normal controls, as measured by thin layer chromatography, high-pressure liquid chromatography, and/or mass spectrometric techniques. in the absence of molecular analysis or where unknown novel mutations are detected, urinary sulfatides testing is used to confirm MLD diagniosis following ARSA activity. Because urine production is highly variable, urinary sulfatide excretion is referenced on the basis of urinary excretion in 24 hours or to another urinary component such as creatinine. (Gomez-Ospina, 2006)

Table B2 shows further tests that can be indicative of MLD, but that alone do not provide a definitive diagnosis.

Table B2: Additional diagnostic tests for MLD

Test	Description	Limitations
MRI or CT scan	Demyelination of the CNS is evident on brain MRI or computed tomography (CT) initially as symmetric periventricular and subcortical T2 white matter prolongation (Wang et al., 2011) Tigroid pattern may be evident in severe cases (Kono et al., 2008) Neuroimaging MRI scoring method may serve as a quantitative biomarker of disease severity (Eichler et al., 2009)	Age (white matter is often not diagnostically visible in infants), not sufficient to rule out or confirm MLD
Ultrasound	Sulfatide deposition in the gallbladder can be visible on abdominal ultrasound (Ferreira and Gahl, 2017, Gomez-Ospina, 2006, Wang et al., 2011)	Not sufficient to rule out or confirm MLD
Nerve conduction studies	Nerve conduction velocities (NCVs) are slowed, reflecting peripheral demyelination and neuropathy (Ferreira and Gahl, 2017, Gomez-Ospina, 2006, Wang et al., 2011)	Not confirmatory/ unique to MLD patients
Lumbar puncture for CSF	Increased cerebrospinal fluid (CSF) protein levels in earlier onset MLD patients	
Hearing and vision	Brainstem auditory evoked response (BAER) and visual evoked potential (VEP) testing demonstrate impairment of hearing and vision (Ferreira and Gahl, 2017, Gomez-Ospina, 2006, Wang et al., 2011)	
Nerve and/or brain biopsy	Metachromatic lipid deposits in nerve or brain can also indicate MLD (Ferreira and Gahl, 2017, Gomez-Ospina, 2006, Wang et al., 2011)	Invasive testing, not often performed for diagnosis

Overview of current treatment

There is currently no approved treatment for MLD; available treatments only alleviate the burden of symptoms of the disease and none of them have proven to halt disease progression or prevent the fatal outcome.

Best supportive care (BSC)

BSC aims to manage disease complications and maintain quality of life but does not target the root cause of the progressive motor and cognitive decline. Current supportive therapies include physical therapy to maintain mobility, muscle relaxant medications to reduce spasticity, pain management, management of skeletal deformity, respiratory physiotherapy to manage pulmonary infections, anti-convulsant drugs to control seizures, and anti-

psychotic medications to control psychiatric symptoms, as well as dietary support, enteral nutrition through a feeding tube in cases of dysphagia, and family and psychological counselling (see Appendix A). (Gomez-Ospina, 2006)

Allogeneic haematopoietic stem cell transplantation (HSCT)

Allogeneic HSCT has been used in limited clinical circumstances for the treatment of MLD patients. However, reported outcomes in early onset MLD (i.e. LI and EJ) patients treated with HSCT have been inconclusive in showing an impact on motor and cognitive decline, possibly due to donor cells being unable to produce supraphysiological levels of ARSA enzyme. Indeed, the replacement of ARSA deficient host cells by ARSA producing donor cells is too slow relative (resulting in a delay estimated at 12–24 months until treatment effect) to the pace of disease progression in early-onset MLD patients, making allogeneic HSCT unsuitable for symptomatic EJ patients or pre-symptomatic patients with LI patients. (Beerepoot et al., 2019, Cable et al., 2011, de Hosson et al., 2011, Ding et al., 2012, Krägeloh-Mann et al., 2013, Smith et al., 2010, Solders et al., 2014)

Allogeneic HSCT is also associated with risks for serious complications, such as graft-rejection, graft versus host disease (GVHD) or complications derived from intense multiagent conditioning regimens. (Martin et al., 2013, Boucher et al., 2015) In addition, allogeneic HSCT carries limitations due to the need to find a matched donor which may delay treatment and compromise the likelihood of a positive outcome due to disease progression.

Currently in clinical practice, the use of allogeneic HSCT has been limited to MLD patients with late-onset variants (i.e. LJ and adult patients), given the slower rate of disease progression in the early stages and the lack of treatment alternatives.

Intrathecal ERT

Enzyme replacement therapy as a treatment for MLD remains an experimental approach with significant limitations. (Sevin et al., 2007) Traditionally, ERT has been administered by IV infusion, and has been shown to be effective for several lysosomal storage disorders without involvement of

the CNS. (Stroobants et al., 2011) For lysosomal storage diseases that involve the CNS, such as MLD, the main challenge is targeting supraphysiological doses of the enzyme to the defective neuronal and glial cells within the brain. A Phase I/II clinical trial using IV recombinant ARSA (HGT-1111) did not show clinical benefit in subjects with LI MLD (Clinicaltrials.gov, NCT00681811) and was terminated. In another completed trial, regular doses of intrathecal (IT) rhARSA (HGT 1110, SHP611) given to symptomatic LI MLD patients showed only limited benefit in attenuating disease progression (ClinicalTrials.gov, NCT01510028, Dali, 2015). A new Phase II study was commenced recently to evaluate the same rhARSA DP (SHP611) via an IT drug delivery device, with higher and more frequent dosing over a longer period of time (Clinicaltrials.gov, NCT03771898).

In conclusion, the absence of effective therapies leads to a high unmet medical need for all MLD patients, particularly in the youngest patients who suffer from the most aggressive LI and EJ variants of the disease. This warrants the development, registration and provision of access to innovative therapeutic approaches such as OTL-200 as soon as possible for the benefit of MLD patients.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Delay from symptom onset to diagnosis

Difficulties in diagnosis, resulting in a delay from onset of symptoms to diagnosis and treatment, is a particular problem in clinical practice, because it results in misdiagnoses and delays in patients being able to access suitable treatment. As noted in Section 8.2, diagnosis of MLD disease is based on laboratory testing following clinical suspicion. Due to the low clinical awareness of the disease and non-specific initial symptoms there can often be a delay in clinical suspicion and diagnosis.

The caregiver study (Pang et al., 2020) reported an average delay of 14.5 months from the onset of symptoms to diagnosis. Similarly, the caregiver (Harrington et al., 2019) reported the mean time from onset of symptoms to

diagnosis was 1.1 years for LI patients and 2.9 years for juvenile patients. (Harrington et al., 2019) It is anticipated that with the approval of OTL-200, there would be an increased awareness of MLD which may translate in earlier diagnosis and ultimately better care.

Rarity of disease

The biggest issue concerning clinical practice is the rarity of MLD disease and the highly-specialised nature of the care and management required. This means that only a small number of very specialised centres as well and healthcare professionals have experience in managing such a rare condition.

Uncertainty in best practice

There is no real uncertainty about best practice in the management of MLD disease, either in the UK or elsewhere. Clinical practice in different countries are very similar, as the international guidelines referred to in Section 8.1 demonstrate. Any variations in care that exist can be addressed by concentrating care in a small number of qualified specialist centres, where specialist expertise and the full multi-disciplinary team are available.

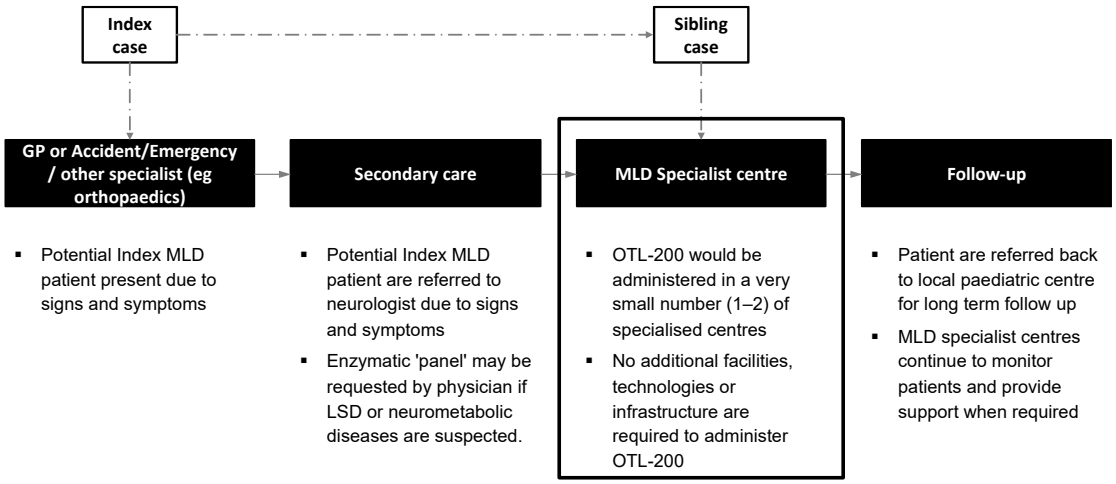
Orchard Therapeutics is in discussions with various stakeholders within the clinical community for the development of several disease awareness and early diagnosis initiatives (including several new-born screening pilot projects), designed to promote early diagnosis of patients with MLD disease. If successful, these initiatives would lead to improved clinical outcomes as a greater proportion of patients being diagnosed in the pre-symptomatic stage of disease.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

As described in Section 8.1, it is anticipated that if commissioned by NHS England, OTL-200 will be administered in at least one of the three paediatric LSD specialist centres in UK. As all three centres have experience in delivering allogeneic HSCT for other neurometabolic diseases, changes to the

existing clinical care pathway are expected to be minimal and will not involve significant alteration to the current service provision by NHS England. Nevertheless, the introduction of OTL-200 will enable patients have a standardised and centralised access to multi-disciplinary and specialist care within the existing Lysosomal Storage Disorder (LSD) network leading to better care and improved outcomes for patients.

Figure B7: Pathway of care for patients treated with OTL-200



8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a ‘step-change’ in the management of the condition.

Step-change in the management of MLD

MLD is a devastating neurodegenerative genetic condition. After initially developing normally, children with MLD gradually lose their acquired speech, cognitive and motor skills, and the ability to feed themselves. They become bedridden and completely dependent on parents and carers before eventually losing their lives at a very young age.

There are currently no treatment options available specifically to treat MLD and none that correct the underlying biological cause of the condition. As noted in section 8.2, current care addresses symptoms only. The available management options consist of supportive or palliative care, which includes

both medication and other interventions to relieve symptoms, maintain function and health-related quality of life.

MLD therefore represents a significant unmet medical need which is addressed by OTL-200, the first and only treatment approved for the treatment of patients with PS LI, PS EJ and ES EJ forms of MLD.

Treatment effects observed in gross motor function, cognition, brain imaging and peripheral nervous system in PS LI, PS EJ and ES EJ MLD subjects show that OTL-200 provides meaningful clinical benefits in the treatment of pre-symptomatic and early-symptomatic stages of the disease. (Orchard Data on file, 2019a)

In addition to providing direct clinical benefits to the patient, OTL-200 is anticipated to benefit families and carers by improving wellbeing and reducing time spent caring. A reduction in the length and intensity of caring may also reduce the risk of mental health problems and family difficulties.

Autologous stem cell therapy

As outlined in section 2.2., OTL-200 is an innovative gene therapy targeting the root cause of MLD by correcting the genetic defect in MLD patients' own $CD34^+$ HSPCs with a single intervention. (Libmeldy SmPC, 2020)

The effects of OTL-200 are durable and stable peripheral engraftment of genetically modified cells was observed from 1-month post OTL-200 administration in all evaluable patients. A persistent vector copy number (VCN) was also observed in $CD34^+$ cells isolated from the bone marrow throughout the follow-up period. These biological findings demonstrate a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting the long-term production of ARSA and resulting long-term clinical benefit.

These results are further supported by the comprehensive data package for OTL-200, comprising data from patients in the IDS with a median follow-up of over 3 years, including two LI patients with more than 7 years of follow up.

Advance the field of gene therapy

As this is the first *ex vivo* gene therapy for a neurological condition, UK clinicians have suggested that this paves the way for the future treatment of other neurological conditions, which not been possible before now (see Section 13.6 for more details).

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

As mentioned in Section 8.4., changes to the current NHS service are not anticipated. OTL-200 will be administered in at least one of the paediatric LSD expert tertiary treatment centre with experience in HSCT that has been JACIE accredited, and further accredited as a qualified treatment centre by Orchard Therapeutics. It is anticipated that OTL-200 will fit into the treatment pathway already followed for HSCT (see Figure B7: Pathway of care for patients treated with OTL-200).

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

OTL-200 is an *ex vivo* autologous $CD34^+$ HSPC gene therapy aiming to correct the genetic defect in MLD patients' own HSPCs. The treatment process follows the same steps as HSCT for other diseases comparable tests/investigations or administration requirements are needed. Some main activities not currently part of usual MLD clinical practice but that would be necessary for OTL-200 treatment (these services are already in place in the expert centres but not part of MLD clinical practice since allogeneic HSCT is not used in these patients) include:

- Cell collection (by highly specialised professionals), already in place via NHS Blood and Transplant Service (NHSBT) or other relevant local services.

- Non-malignant HSPC transplantation, already conducted and set up in a number of hospitals within the UK for other diseases.
- Monitoring of transplanted patients by the consultant haematologist (i.e. transplant team) for the first 2 years as part of the UK stem cell transplant protocols.
- Ability to access patients through their referral networks; as well as to implement necessary Orchard Therapeutics's operating processes and systems.

Concurrently with the conditioning regimen, and prior to treatment with OTL-200, it is recommended that patients receive treatment with prophylaxis for veno-occlusive disease (VOD) and related endothelial injury complications i.e. transplant-associated thrombotic microangiopathy (TA-TMA) or atypical haemolytic uremic syndrome (aHUS), in line with local guidelines. (Libmeldy SmPC, 2020)

During clinical development, anti-ARSA antibodies (AAA) were reported in four subjects. Titers were generally low, and all events resolved spontaneously or after treatment with rituximab. No obvious impacts were noted on the clinical efficacy or safety outcomes in these patients. Furthermore, AAA are not anticipated to interfere with the functionality of ARSA activity in brain due to the limited ability of antibodies to cross the blood-brain barrier. (Libmeldy SmPC, 2020)

Monitoring of AAA is nonetheless recommended prior to treatment, between 1 and 2 months after gene therapy, and then at 6 months, 1 year, 3 years, 5 years, 7 years, 9 years, 12 years, 15 years post treatment. (Libmeldy SmPC, 2020)

In a case of disease onset or significant disease progression, additional AAA monitoring is also recommended. (Libmeldy SmPC, 2020)

If the presence of AAA is confirmed (i.e. upon second/repeat test), a short treatment with rituximab can be considered, at the discretion of the treating physician, taking into consideration the AAA titers identified, clinical manifestations of the disease (neurological symptoms, delayed milestones) or

other autoimmune manifestations for which there is an indication for a B-cell depletion treatment. (Libmeldy SmPC, 2020)

Patients in whom AAA are cleared following a course of rituximab should continue to be regularly monitored for the presence of antibodies for at least 1 year. (Libmeldy SmPC, 2020)

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

The infrastructure and expertise to proceed with autologous transplantation is already in existence through NHS apheresis service and transplant centres. Orchard Therapeutics is committed to investing time and resources to support and upskill the relevant cross-functional teams within the treatment centres. No other additional facilities, technologies or infrastructure will be required.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Patients treated with OTL-200 may still require a level of symptomatic care; however, given the potential of OTL-200 to prevent onset of disease symptoms or slow down disease progression, it is anticipated that reliance on symptomatic care would be reduced, and, if patients are treated early enough, it is possible that the need for symptomatic care could be avoided altogether. Detailed below are some of the interventions, technologies or equipment which will be reduced or avoided leading to potential significant cost savings to the health system

- Insertion of gastrotomy tube for feeding in patients with swallowing difficulties which tends to occur during the end stage of the disease
- Saliva suction machine to remove saliva
- Hospital stay to manage episodes of ill-health (e.g. chest infections)
- Anti-epileptics, pain medications and antibiotics

- Wheelchairs, walkers as well as home and car adaptations.

Section C — Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

Clinical study overview:

- The safety and efficacy of OTL-200 have been demonstrated in a comprehensive clinical programme involving 35 patients treated in two clinical studies (the registrational study 201222 and the clinical study 205756) and three Expanded Access Programs (EAPs). (Orchard Data on file, 2019b, Orchard Data on file, 2019c)
- 29 of the 35 patients in the clinical programme were treated with the fresh formulation of OTL-200 (OTL-200-f) and six patients were treated with the cryopreserved formulation (OTL-200-c).
- The fresh formulation data include 20 patients treated in registrational study 201222 and nine patients treated in three expanded access programmes (EAPs). Registrational Study 201222 and the EAPs have a similar study design and were conducted by the same team at the same centre, and these patients have been combined to make the Integrated Data Set (IDS; n=29). (Orchard Data on file, 2019a)
- Efficacy results from patients treated with OTL-200-f demonstrated that the patients who benefitted from treatment were:

- Late Infantile and Early Juvenile patients treated pre-symptomatically (PS LI and PS EJ) (i.e. before clinical manifestations of the disease); and
- Early Juvenile patients with early clinical manifestations of the disease (ES EJ). (i.e. still had the ability to walk independently and before the onset of cognitive decline)

- As such, the CHMP approved indication for OTL-200 is restricted to these patients.
- Hence, this submission will present efficacy data from a post-hoc analysis focussed on the patients within the IDS who fall within the indication. In total [redacted] out of 29 patients in the IDS were included in this analysis:
  - [redacted] patients with pre-symptomatic Late Infantile (PS LI) MLD, [redacted] patients with pre-symptomatic Early Juvenile (PS EJ) MLD and [redacted] patients with early-symptomatic Early Juvenile (ES EJ) MLD (hereafter referred to as the Indicated Population, IP).
- The [redacted] patients in the IDS not included in the post hoc efficacy analysis would not be eligible for treatment based on the indication which received positive opinion from the CHMP.
- In addition, preliminary efficacy data from the six patients treated with the cryopreserved formulation will also be presented. (Orchard Data on file, 2019e)

Figure C1: [redacted]

- To provide a comprehensive overview of the safety of OTL-200, the safety data presented in this section are from all patients in the clinical programme (i.e. all 29 patients treated with OTL-200-f and the 6 patients treated with OTL-200-c).
- Although the studies had no comparator for ethical and practical reasons, the studies used data from age- and disease subtype-matched patients in the NHx study run by the same centre (OSR-TIGET) as a comparator group. Analysis using data from untreated affected siblings in the NHx study were also undertaken.

Summary of efficacy data from the Indicated Population (IP)

- The data from the IP show that OTL-200, provides meaningful clinical benefits in the treatment of PS LI, PS EJ and ES EJ patients.(Orchard Data on file, 2019b)

    1. Engraftment:

        - Durable and stable peripheral engraftment of gene-corrected cells was observed from 1 month post OTL-200 administration in all subjects treated, as indicated by %LV+ values well above the

protocol-defined target of 4% and persistent VCN in CD34+ cells isolated from the BM and PB throughout the follow-up period.

- Similar engraftment efficacy has been shown for %LV+ values and VCN in CD34+ cells in BM and PB with both OTL –200-f and OTL- 200-c formulations.

- These findings demonstrated a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting microglial reconstitution and the long-term production of ARSA.

2. ARSA activity:

- Reconstitution of ARSA activity in the haematopoietic system and CNS was observed in all subjects in the indicated population, with ARSA levels in PBMCs and CSF reaching values within the normal reference range by 3 months post-treatment and remained stable within or above the normal range throughout the duration of the follow-up.

- These results provide indirect evidence that genetically modified cells, effectively migrated to the CNS, engrafted, and produced ARSA enzyme activity within or above the normal range.

3. Gross Motor Function:

- When compared to age-matched natural history (NHx) patients within the same disease subtype, PS LI, PS EJ and ES EJ MLD subjects treated with OTL-200 showed normal motor development, stabilisation, or delay in the rate of progression of motor dysfunction as measured by GMFM total score (%).

  - [redacted]

  - [redacted]

treatment differences for PS LI and PS EJ were statistically significant in favour of OTL-200.

- [redacted]

- Gross motor function results assessed by GMFC-MLD were consistent with GMFM results. In summary, all OTL-200 treated patients in the indicated population, either stabilised at the same GMFC score throughout the follow-up period or had a slower decline in GMFC score compared to age-matched NHx patients or matched siblings.

4. Cognitive function:

- Developmental quotient (DQ) and age equivalent scores were used as exploratory analyses of cognitive function and provide further evidence that the high levels of engraftment and enzymatic reconstitution translate into relevant treatment effects on key domains that are hallmarks of MLD.

- Performance DQ scores were above 55 for [redacted] evaluable OTL-200 treated PS LI, PS EJ and ES EJ subjects at Year 2 and Year 3.

  - [redacted]

  - [redacted]

  - [redacted]

[redacted]

- Age-equivalent scores showed normal acquisition of cognitive skills in the majority of treated LI and EJ subjects at chronological ages at which untreated NHx subjects showed severe cognitive impairment.

5. Brain MRI:

- Brain MRI results suggest that treatment with OTL-200 prevents, stabilises, or markedly delays the progressive demyelination and atrophy typically observed as a hallmark of MLD.
- [redacted]
- [redacted]
- [redacted]

6. Overall survival (OS):

- Analysis of overall survival suggests that treatment with OTL-200 improves overall survival in PS LI MLD compared with untreated patients and matched siblings. [redacted]

- [redacted]
- [redacted]

7. Composite quality of life-adjusted survival endpoints:

- Results from analyses of severe motor impairment-free survival (sMFS) demonstrate that treatment with OTL-200 prevents or delays progression to the end-stage of disease and early death.
- [redacted]
- [redacted]

8. Treatment effects on the peripheral nervous system:

- Treatment effects on peripheral neuropathy demonstrates that OTL-200 reduces demyelination in the peripheral nervous system, which is a major contributor to the gross motor dysfunction and generally refractory to therapeutic interventions.
- [redacted]
- [redacted]

Summary of efficacy data from patients treated with OTL-200-c

- The cryopreserved formulation of OTL-200 (OTL-200-c) will be the commercially available formulation. Preliminary clinical data from Study 205756 (Orchard Data on file, 2019e) support the *in vitro* analytical comparability and *in vivo* comparability data between the fresh and cryopreserved formulations of OTL-200.
- Peripheral engraftment of gene-corrected cells was observed from [redacted] subjects treated with OTL-200-c. The %LV+ transduced cells and VCN values were within the range observed in subjects treated with the fresh formulation.
- Similarly, ARSA activity profiles in PBMCs and CSF were consistent with results observed in subjects treated with the fresh formulation.
- This clinical experience with the fresh product indicates that patients treated with the cryopreserved formulation will achieve similar clinical outcomes to those observed in patients treated with the fresh formulation.

Summary of safety data from all patients in the clinical programme

- OTL-200 was well-tolerated with no treatment-related serious adverse events in patients treated with either the fresh or cryopreserved

formulations of OTL-200. (Orchard Data on file, 2019c, Orchard Data on file, 2019e)

- The most common adverse events observed were consistent with the known safety profile of busulfan, symptoms of MLD, or events expected during childhood.
- There were three deaths in the clinical programme, none of which were related to OTL-200. Two of the deaths occurred in patients who would be ineligible for treatment per the approved indication. The other death was due to ischemic cerebral infarction and considered unrelated to OTL-200 or MLD.
- There were no cases of positive replication competent lentivirus (RCL), malignancy or AEs indicative of oncogenic transformation. Neither was there any evidence of abnormal clonal proliferation in any patient treated with OTL-200.
- In conclusion, the safety findings in subjects treated with OTL-200 are in line with what would be expected in subjects who have undergone busulfan conditioning and haematological reconstitution.

9.1 Identification of studies

A systematic literature review (SLR) was carried out to identify current clinical evidence on the effectiveness, safety and costs of treatments for MLD, including OTL-200, in children. (Kleijnen Systematic Reviews Ltd., 2020 Data on file) The SLR was conducted by Kleijnen Systematic Reviews Ltd, an ERG for NICE appraisals, and was overseen by the Professor of Systematic Reviews.

The SLR addressed the following specific research questions:

- What is the effectiveness and safety of *ex-vivo* autologous lentiviral gene therapy OTL-200 for the treatment of MLD in children (≤ 17 years)?

- What is the effectiveness and safety of standard/supportive care and other therapies (allogeneic HSCT) for the treatment of MLD in children (≤ 17 years)?
- What are the costs of treatments for MLD in children (≤ 17 years)?

The SLR was conducted before the final indication was determined, hence the inclusion of children up the age of 17 years.

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

The methodologies of the Cochrane Collaboration and the Centre for Reviews and Dissemination were followed. Literature searches were conducted across a range of databases (including MEDLINE and Embase) from inception to May 2020, with no date, language, or publication limits. Relevant clinical trial registries and conferences were searched. The reference lists of included studies and other systematic reviews were checked for further studies. Randomised controlled trials (RCTs) and prospective single arm or cohort studies assessing the clinical effectiveness or safety of OTL-200, allogeneic HSCT or standard/best supportive care in children (≤ 17 years) with MLD were included. The risk of bias was assessed for each study and a narrative synthesis with accompanying tables and figures was used to summarise the findings. At the time of initiating the SLR, the draft indication still included Late Juvenile (LJ) MLD patients, hence why the SLR includes evidence from MLD children up to 17 years and those treated with allogeneic HSCT.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

The U.S. National Institutes of Health clinical trials registry and results database (clinicaltrials.gov) and the Orphanet Clinical trials Search (Internet) were searched to identify ongoing studies or results that may not have been

published. The reviewer was unable to search the WHO International Clinical Trials Registry Platform (ICTRP) as access is currently restricted to WHO staff only, for the duration of the COVID public health emergency.

The manufacturer was also contacted and asked to provide any unpublished studies available.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1: Selection criteria used for published and unpublished studies

Inclusion criteria	

Population	Patients with early-onset metachromatic leukodystrophy (MLD), i.e. diagnosed aged ≤ 17yrs[4] (as per draft indication before change to current indication at CHMP opinion on 15th October 2020).
	Subgroups of interest within the main population included:
	• Symptomatic MLD
	• Pre-symptomatic MLD
	• Late Infantile MLD
	• Juvenile MLD
	  ○ Early Juvenile
	  ○ Late Juvenile
	Where populations included a mixed age group including patients with onset of disease >17yrs, studies were only included if data were reported separately for those with early-onset disease (i.e. symptoms appearing ≤ 17yrs).

[4] At the time of initiating the SLR, the draft indication still included late juvenile MLD patients, hence why the SLR includes evidence from MLD children up to 17 years and those treated with allogeneic HSCT. The current indication with positive CHMP opinion on 15th October 2020, no longer includes LJ patients.

Interventions	The intervention of interest was *ex-vivo* autologous lentiviral gene therapy, specifically OTL-200 (OTL-200). The following were included: • OTL-200 treatment arms in single arm studies • OTL-200 treatment arms in RCTs and cohort studies making a comparison with a relevant comparator treatment of interest. Comparator treatments of interest were: • Standard care/best supportive care/usual care* • Allogeneic haematopoietic stem cell transplantation (HSCT)[5] The following were included: • Comparator treatment arms in single arm studies • Comparator treatment arms in RCT and cohort studies comparing the comparator treatments with each other or against the intervention of interest (i.e. OTL-200)

[5] At the time of initiating the SLR, the draft indication still included late juvenile MLD patients, hence why the SLR included allogeneic HSCT as a comparator given its use in this subset of patients. As the current indication with positive CHMP opinion on 15th October 2020, no longer has late juvenile patients, allogeneic HSCT will not be a comparator for OTL-200 given its not a treatment option in this patient group

Outcomes	Studies must report at least one of the following specific outcomes which are relevant to the NICE scope (also based on outcomes from OTL-200 clinical studies): Mortality: • Overall survival (OS) expressed as a hazard ratio (HR), median time to event, or proportion (n/N; %) of patients surviving (if only number of deaths are reported this will be used to calculate the number surviving where possible) Progressive disease: • Proportion (n/N; %) of individuals with progressive disease (PD) Median (range) time to progressive disease (PD) Motor function: • Proportion (n/N; %) of individuals with severe motor impairment • Median (range) time to severe motor impairment • Mean (SD)/median (range) age at time of severe motor impairment • Mean change (SD) from baseline in motor function measured using the following tools: • Gross Motor Function Classification System (GMFCS) • Gross Motor Function Measure (GMFM) • Gross motor function classification (GMFC-MLD) Neurological function: • Mean change (SD) from baseline in nerve conduction velocity (NCV) • Mean change (SD) from baseline in total score for brain magnetic resonance (MR) imaging (Loes score) and sub-scores (demyelination, atrophy and tigroid scores). Cognitive function: • Proportion (n/N; %) of individuals with cognitive impairment • Median (range) time to cognitive impairment • Mean change (SD) from baseline in neurocognitive function measured using the Intelligence Quotient (IQ) • Mean change (SD) from baseline in neurocognitive function measured using the Developmental Quotient (DQ) • Mean change (SD) from baseline in the Expressive Language Function Classification Arylsulfatase (ARSA) activity: • Change from baseline in ARSA activity in total peripheral blood mononuclear cells (PBMC) • Change from baseline in ARSA activity in leukocytes • Change from baseline in peripheral blood (PB) CD14+ cells • Change from baseline in cerebrospinal fluid (CSF) Health related quality of life (HRQoL): • Mean change (SD) from baseline in Caregiver Observed Metachromatic Leukodystrophy Functioning and Outcomes Reporting Tool (COMFORT) • Mean change (SD) from baseline in the (EQ-5D)

	Safety:
	• Proportion (n/N; %) of patients experiencing the following safety outcomes (to include treatment related events, treatment emergent events, and all events, where separate data are available):
	  ○ Any adverse event
	  ○ Serious adverse events
	  ○ Fatal adverse events
	  ○ Any specific event occurring in ≥ 5% of patients in any one study arm
	Economic:
	• Health-related quality of life
	• Utilities
	• Costs and use of resources
	• For economic evaluations:
	  ○ Location of study
	  ○ Summary of model and comparators
	  ○ Patient population (key characteristics, average age)
	  ○ Costs (intervention and comparator)
	  ○ Patient outcomes (clinical outcomes, quality adjusted life expectancy (QALYs), life expectancy)
	  ○ Results (annual cost savings, annual savings per patient, incremental cost per QALY (ICER))

Study design	The following types of studies were included: • RCTs • Prospective or retrospective single arm studies with > 5 participants • Prospective or retrospective cohort studies with > 5 participants • Any type of economic evaluation (cost-effectiveness analysis (CEA), cost only comparison, budget impact analysis (BIA) or cost of illness (COI) study
Language restrictions	Searches were not limited by language.
Search dates	Databases from database inception to May 2020. Conferences 2018-2020. ClinicalTrials.gov (NIH): Up to 19 May 2020. Orphanet Clinical trials search (Internet): up to 04 June 2020.
Exclusion criteria	
Population	Studies not reporting data on patients with early-onset metachromatic leukodystrophy (MLD), i.e. diagnosed aged ≤ 17yrs, including those where populations included a mixed age group including patients with onset of disease >17yrs, and data were not reported separately for those with early-onset disease (i.e. symptoms appearing ≤ 17yrs). Studies with ≤ 5 participants.

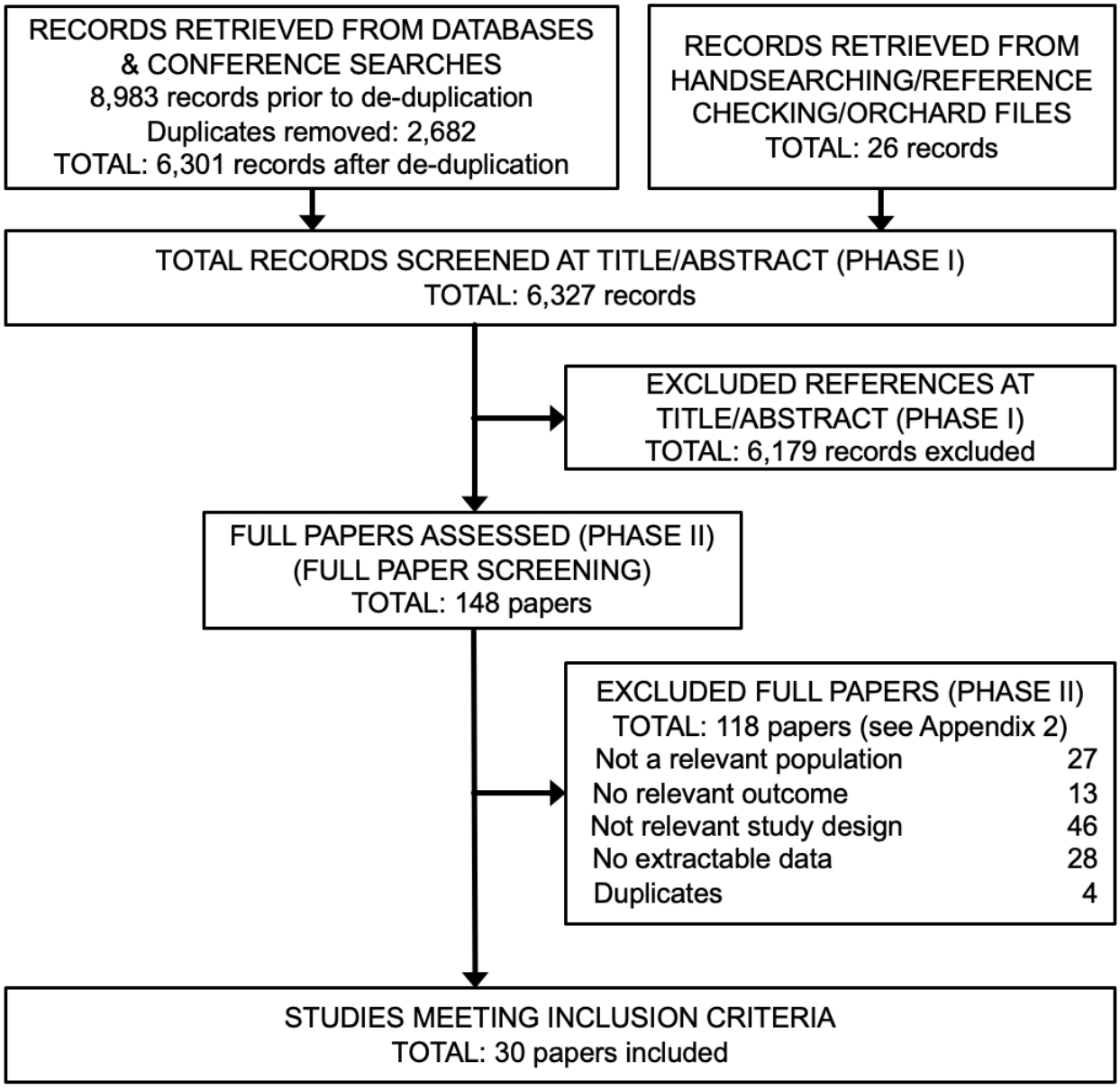
Interventions	Studies not reporting data on the listed interventions or comparators.
Outcomes	All other outcomes. Vector clone number (VCN) and % lentivirus (LV) + clone are outcomes only relevant for OTL-200 gene therapy, these will not be recorded as key outcomes.
Study design	All other study designs including, but not limited to, case reports, cross-sectional studies, animal studies or biochemical or cellular level investigations.
Language restrictions	Searches were not limited by language.
Search dates	None.

* Best supportive/symptomatic care can include any of the following including combinations of any of the following: Management of dystonia, infections, seizures (if required) or secretions; pain relief/sedative drugs (if required); feeding support (including gastrostomy); psychological and social support (including specialist schooling); coordination of the multidisciplinary team and community care; genetic advice and planning; and end of life care.

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

A total of 6,327 titles and abstracts were screened and full paper copies of 148 citations selected for further scrutiny. Thirty papers reporting on a total of 14 studies (12 clinical effectiveness/safety studies and two economic studies) were selected for inclusion in the review. All were single arm studies except for three studies which included comparison data. Most gathered data retrospectively, however, OTL-200 data were gathered prospectively. All the studies were judged at high risk of bias except for Orchard Therapeutics Study 201222, which was judged as at an unclear risk of bias. Of the 30 papers selected for inclusion, 24 were published.

Figure C2: Summary of study selection according to PRISMA



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

The same inclusion and exclusion criteria listed in Table C1 for published studies was also used for selecting unpublished studies.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Of the 30 papers selected for inclusion, four were unpublished.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Unpublished studies of OTL-200 are shown in Table C2. The safety and efficacy of the fresh formulation of OTL-200 (OTL-200-f) have been evaluated in a clinical development programme consisting of one registrational study (Study 201222) (Clinicaltrials.gov NCT01560182) and three expanded access programmes (EAPs) consisting of two compassionate use programmes (CUPs) (CUP207394 and CUP206258) and one hospital exemption programme (HE 205029). The cryopreserved formulation of OTL-200 (OTL-200-c) is being evaluated in Study 205756 (ClinicalTrials.gov NCT03392987).

A study to evaluate the efficacy and safety of the cryopreserved formulation of OTL-200 in patients with the LJ variant of MLD began in June 2020 (Clinicaltrials.gov NCT04283227); no results have been reported yet for this study.

There are no studies that compare OTL-200 treatment directly with either best supportive care (BSC) or other treatment options for MLD.

Table C2: List of unpublished OTL-200 studies

Data source	Study number (status)	Study title	Population	Intervention and comparator
Study 201222 CSR	Phase I/II trial (Study 201222 TIGET-MLD, fresh product formulation) (enrolment closed, follow-up ongoing)	Open-label, non-randomised, single-arm clinical trial evaluating the safety and efficacy of OTL-200 in patients with pre-symptomatic LI or pre- or early-symptomatic EJ MLD	Patients with pre-symptomatic LI or pre- or early-symptomatic EJ MLD; n=20	Intervention: OTL-200 Comparator: Age and disease variant-matched natural history population
MAA Module 2.7.3	EAP CUP207394 (fresh product formulation; enrolment closed, follow-up ongoing)	Expanded Access Programme	One patient (symptomatic EJ variant of MLD) treated with OTL-200 in 2013	As for Study 201222.
MAA Module 2.7.3	EAP HE205029 (fresh product formulatio;n enrolment closed, follow-up ongoing)	Hospital Exemption	Three early-onset MLD patients (all pre-symptomatic LI variant), treated with OTL-200 in 2016	As for Study 201222.
MAA Module 2.7.3	EAP CUP206258 (fresh product formulation; enrolment closed, follow-up ongoing)	Expanded Access Programme	Five early-onset MLD patients (four LI, one EJ variant), all pre-symptomatic at the time of treatment, treated with OTL-200 in 2016	As for Study 201222.
Study 205756 ab-breviated CSR	Phase II trial (Study 205756, cryopreserved product formulation) (active but no longer enrolling patients)	Open-label, single-arm study evaluating the efficacy and safety of the cryopreserved formulation of OTL-200 in 10 patients with pre-symptomatic LI or pre- or early-symptomatic EJ MLD	Patients with pre-symptomatic LI or EJ MLD; n=6 (as of the last data-cut)	Intervention: OTL-200 Comparator: Age and disease variant-matched natural history population

9.3.2 State the rationale behind excluding any of the published studies listed in table C2.

None of the relevant studies were from published results.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies. A separate table should be completed for each study.

Study 201222 (registrational study in fresh formulation)

Study 201222 is a non-randomised, open-label, prospective, comparative (non-concurrent control), single-centre study in children with early-onset MLD (LI or EJ variants), as assessed by arylsulfatase A (ARSA) enzymatic activity and genetic analysis. (Orchard Data on file, 2019d) The original study was planning to enrol and treat eight subjects (pre-symptomatic LI and pre- or early symptomatic EJ). The sample size and proportion of pre-symptomatic LI and pre-symptomatic or early symptomatic EJ subjects were revised multiple times during the course of the study following Scientific Advice procedures with European Medicines Agency (EMA) and emerging results on efficacy and safety. The final study design included a sample size of 20 early-onset MLD subjects.

After signature of the informed consent, subjects were enrolled in the study. There are four study phases:

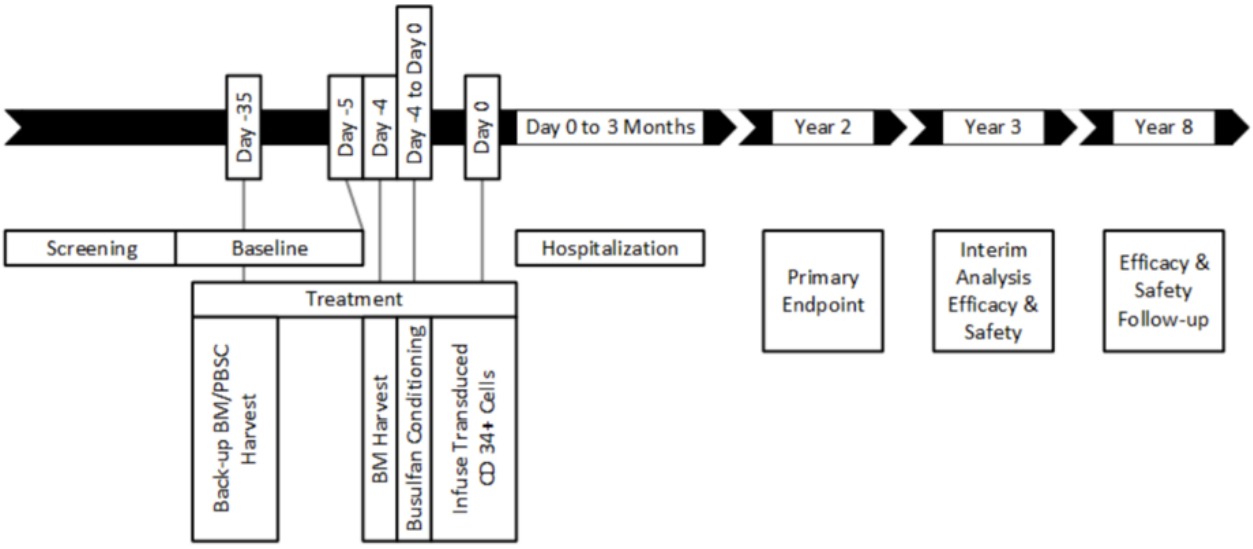
Screening phase, during which the eligibility criteria required by the clinical protocol for the subject's enrolment are assessed and evaluated;

Baseline phase, once eligibility is confirmed, the Baseline phase commences from the time of the CD34^{+} cell harvest for DP manufacture and backup. The Baseline phase ends on the day before the commencement of the busulfan conditioning. Clinical and instrumental tests aimed at defining baseline disease status are performed as close as possible to the Treatment phase. Under certain circumstances, baseline assessments may be performed at screening, based on the clinical judgement of the investigator.

Treatment phase (Day -5 to Day 1). The treatment phase includes haematopoietic stem-cell harvest for drug product (DP) manufacture and back-up, administration of a sub-myeloablative or myeloablative busulfan conditioning regimen, and the administration of the fresh formulation of OTL-200. The phase commences with the start of busulfan conditioning (Day -5 to Day -2), and completes at the end of the infusion of OTL-200 on Day 0.

Follow-up phase, from end of treatment infusion until 8-year follow-up visit, during which all study endpoints will be assessed.

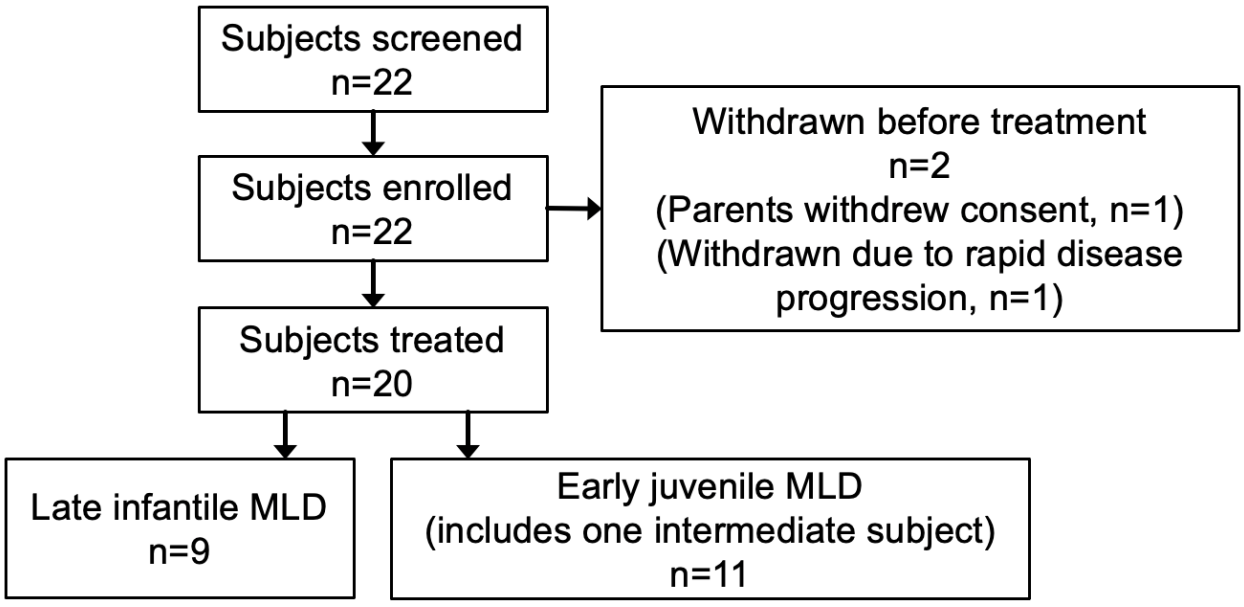
Figure C3: Study 201222 design



A total of 22 early-onset MLD subjects were screened and enrolled into Study 201222, with two subjects withdrawn prior to treatment. Among the 20 subjects treated with gene therapy were:

- Nine subjects in the LI MLD subgroup
- 11 subjects in the EJ MLD subgroup (including one subject who was classified as having an 'Intermediate LI/EJ-variant' but was grouped with the EJ variant for analysis purpose*).

Figure C4: Subject disposition for Study 201222



Among all treated subjects (n=20), the median duration of post-treatment follow-up was 4.0 years (range: 0.6 to 7.5 years), and all surviving subjects (n=18) had at least 3 years of post-treatment follow-up as of their last study visit, at the time of the latest data cut-off for interim data analysis (30 March 2018).

- LI subgroup (n=9): 5.4 years (range: 3.0 to 7.5 years)
- EJ subgroup (n=11): 3.5 years (range: 0.6 to 6.6 years)

Two symptomatic EJ subjects treated in Study 201222 died after experiencing rapid disease progression (8 months and 15 months after treatment,

* According to the protocol-defined criteria for classifying MLD subtypes, this subject has two 'R' alleles (which does not fit the definition of either disease variant), a sibling with age of symptom onset between 24 and 36 months, and peripheral neuropathy on ENG assessment. These findings, along with the disease course of the older affected sibling (alive at age 16), which appears milder than the typical LI course and similar to the typical EJ course, suggest that this subject and her older sibling are affected by a clinical variant of intermediate severity between the classical LI and EJ forms. For the purposes of data analysis, this subject has been included in the EJ dataset, as this represents the more conservative approach for evaluating the effect of Libmeldy in this subject.

respectively). In both cases, treatment was initiated after onset of cognitive decline or rapid progression, as such these patients would not have been eligible for treatment as per the approved indication. Neither of these deaths were attributed to the study treatment by the investigators. For more information on these subjects, see Section 9.7.2.1.

Table C3: Methodology for Study 201222

Study name	Study 201222 TIGET-MLD, fresh formulation of OTL-200
Objective	To evaluate the safety and efficacy of OTL-200 in patients with pre-symptomatic Late Infantile (LI) or pre- or early-symptomatic Early Juvenile (EJ) metachromatic leukodystrophy (MLD).
Location	Ospedale San Raffaele - Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy.
Design	Non-randomised, open-label, prospective, comparative (non-concurrent control), single-centre study.
Duration of study	Subjects will be followed up for at least 8 years post-treatment.
Patient population	Children up to 6 years of age with early-onset MLD (LI or EJ variants). The LI variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms in the older sibling(s) ≤ 30 months and/or two null (0) mutant ARSA alleles and /or peripheral neuropathy at electroneurographic (ENG) study. The EJ variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms (in the patient or in the older sibling) between 30 months and 6 years (had not celebrated their 7th birthday), and/or one null (0) and one R mutant ARSA allele(s) and/or peripheral neuropathy at ENG study. Pre-symptomatic clinical status was defined as subjects without neurological impairment (disease- related symptoms), with or without signs of the disease revealed by instrumental evaluations (ENG and brain MRI). Early-symptomatic clinical status (for the EJ variant) was initially defined as subjects identified within 6 months from the first reported symptoms (two EJ subjects were enrolled using this definition: MLD04 under Protocol 2.0, 26Jan2010 and MLD08 under Protocol 3.0, 04Apr2012). Subsequently (Amendment 7, dated 10Dec2013), early-symptomatic EJ subjects were defined as subjects meeting the following two criteria: IQ ≥70 and the ability to walk independently for ≥10 steps. The rationale for this change was to prevent enrolment of subjects who had a rapidly progressive form of the disease as identified at the time of treatment. All LI subjects and some pre-symptomatic EJ subjects were identified after an older sibling had developed symptoms and received an MLD diagnosis, prompting testing in other family members.

Sample size	A total of 22 early-onset MLD subjects were screened and enrolled into Study 201222, with two subjects withdrawn prior to treatment. Among the 20 subjects treated with gene therapy were: • Nine subjects in the LI MLD subgroup • 11 subjects in the EJ MLD subgroup (including one subject who was classified as having an 'Intermediate LI/EJ-variant' but was grouped with the EJ variant for analysis purpose).
Inclusion criteria	Documented biochemical and molecular diagnosis of MLD, based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles, either known or novel mutations. Novel mutations will be analysed with in silico prediction tools and excluded from being known common polymorphisms. In the case of a novel mutation(s), a 24-hour urine collection must show elevated sulfatide levels. Eligible subjects must have EITHER: 1. An older sibling affected by MLD (index case), whose age of symptom onset was ≤ 6 years of age (i.e. had not celebrated 7th birthday). Subjects will be classified as LI, EJ or intermediate LI/EJ based on age of symptom onset in the index case and their ARSA genotype; LI: symptom onset in index case ≤30 months of age and genotype typically 0/0; EJ: symptom onset in index case > 30 months and ≤ 6 years of age with genotype typically 0/R; Intermediate LI/EJ: symptom onset in index case ≤6 years of age but unable to unambiguously characterize index case as LI or EJ • OR 2. If MLD is diagnosed in a pre-symptomatic child without an older affected sibling, (e.g. incidentally or via newborn screening) and the totality of the data available to the investigator strongly suggest that the subject has an early onset variant of MLD likely to benefit from gene therapy, and the subject is ≤ 6 years of age (i.e. has not celebrated 7th birthday), the subject may be considered eligible after discussion and approval by the Orchard Therapeutics medical monitor. Parental/guardian signed and dated informed consent.

Exclusion criteria	Documented HIV infection (positive HIV RNA and/or anti-p24 antibodies). Malignant neoplasia (except local skin cancer) or a documented history of hereditary cancer syndrome. Subjects with a prior successfully treated malignancy and a sufficient follow-up to exclude recurrence (based on oncologist opinion) can be included after discussion and approval by the Medical monitor. Myelodysplasia, cytogenetic alterations characteristic of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), or other serious haematological disorders. Subjects currently enrolled in other interventional trials. Has previously undergone allogeneic hematopoietic stem cell transplantation and has evidence of residual cells of donor origin. Previous gene therapy. Has symptomatic herpes zoster, not responsive to specific treatment. Subjects with a recent history of herpes zoster may be included in the study. In such cases, inclusion, additional monitoring and treatment of the condition must be discussed and approved by the medical monitor. Evidence of active tuberculosis (TB) based upon medical examination, chest imaging and TB testing i.e. QuantiFERON-TB Gold test and microbiological evidence. Subjects with latent tuberculosis, as documented by medical history and/or TB testing may be included in the study if receiving antibiotic prophylaxis (e.g. isoniazid). Inclusion, monitoring and treatment of TB in such subjects must be discussed and approved by the medical monitor. Acute or chronic stable Hepatitis B as evidenced by positive Hepatitis B surface antigen (HBsAg) test result at screening or within 3 months prior to onset of conditioning and/or positive hepatitis B virus (HBV) DNA. Subjects with positive Hepatitis B core antibody due to prior resolved disease may be enrolled, only if a confirmatory negative Hepatitis B surface antigen and negative Hepatitis B DNA test are obtained. Inclusion, monitoring and treatment of hepatitis in such subjects must be discussed and approved by the medical monitor. Presence of positive Hepatitis C RNA test result at screening; subjects who have previously tested positive for antibodies against hepatitis C can be treated, provided they demonstrate absence of ongoing infection using a nucleic acid test with a limit of quantification of ≤ 15 international units/millilitre (IU/mL). Negative test results are required on at least three sequential occasions over a period of at least 4 weeks, after completion of treatment for hepatitis C, with the final test conducted no more than 3 days prior to cell harvest. Inclusion, monitoring and treatment of hepatitis in such subjects must be discussed and approved by the medical monitor. End-organ dysfunction, severe active infection not responsive to treatment, or other severe disease or clinical condition which, in the judgment of the investigator, would make the subject inappropriate for entry into this study. In addition to the potential infections the PI should consider testing for other transmissible infectious agents listed in the European Union (EU) Cell and Tissue Directive as clinically appropriate and results discussed with the medical monitor prior to cell harvest. Subjects with alanine transferase (ALT) > 2x upper limit of normal (ULN) or total bilirubin > 1.5xULN may be included only after discussed and agreed with the medical monitor and considered in the context of the criterion for excluding subjects with other severe disease.

	Isolated elevation of total bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin < 35 percent of total.
Intervention(s) (n = 20) and comparator(s) (n = 0)	Fresh formulation of OTL-200 (OTL-200-f; n=20).
Baseline differences	Not applicable.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Participants followed up via study visits planned for at least 8 years post-treatment. Median duration of post-treatment follow-up was 4.0 years (range: 0.6 to 7.5 years), and all surviving subjects (n=18) had at least 3 years of post-treatment follow-up as of their last study visit, at the time of the latest data cut-off for interim data analysis (30 March 2018). Two symptomatic EJ subjects died after experiencing rapid disease progression (8 months and 15 months after treatment, respectively). In both cases, the symptoms of disease progression typically involved progressive deterioration in motor function, worsening spasticity and inability to feed. These deaths were not attributed to the study treatment by the study investigators. Both subjects would not have been eligible for treatment as per the approved indication
Statistical tests	No formal statistical testing will be performed.
Primary outcomes (including scoring methods and timings of assessments)	Co-primary efficacy endpoints: • Improvement ≥10% in total Gross Motor Function Measure (GMFM) score compared to historical control MLD population • Significant (≥2 SD) increase in residual ARSA activity as compared to pre-treatment values, measured in peripheral blood mononuclear cells (PBMCs) at Year 2 after treatment Primary safety endpoints: • Conditioning regimen-related safety: o Absence of engraftment failure or delayed haematopoietic reconstitution (prolonged aplasia), defined as ANC < 500/μL at +60 days after transplantation, with no evidence of BM recovery, requiring cellular back-up administration. o Absence of conditioning regimen-related toxicity, as determined by a surveillance of clinical (NCI grade ≥ 2) and laboratory (NCI grade ≥ 3) parameters applied in the short- and long-term follow-up of the treated subjects in order to assess the degree of morbidity associated with the conditioning regimen. • Safety of LV-transduced cell infusion: o Short-term safety and tolerability of LV-transduced cell infusion, evaluated on the basis of adverse event (AE) reporting and monitoring of the systemic reactions to cell infusion. The short-term safety of LV-transduced cell infusion consists of the absence of serious adverse events (SAEs) within 48 hours of infusion. o The long-term safety of LV-transduced cell infusion, which was evaluated as the absence of replication competent lentivirus (RCL) and the absence of Abnormal Clonal Proliferation (ACP).

Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy outcomes: • Gross motor function classification (GMFC)-MLD levels at different ages in treated subjects compared to the historical control MLD population. • Nerve conduction velocity (NCV) Index at Year 2 after treatment significantly higher than scores observed in age-matched historical control MLD subjects • Total brain magnetic resonance imaging (MRI) score at Year 2 after treatment significantly lower than in age-matched historical control MLD subjects. • Intelligence quotient (IQ) > 55 (threshold for severe disability) at neuropsychological testing performed at 24-, 30-, and 36-month follow-ups. • Transduced cell engraftment > 4% in PBMC and CD34+ progenitors in bone marrow (BM) (determined as vector copy number (VCN)/cell ≥ 0.04 at quantitative polymerase chain reaction [qPCR], equivalent to 4% assuming a VCN of 1) at Year 1 after transplant. • Correlations between transduced cell engraftment parameters and busulfan exposure: Evaluations of percent lentiviral vector (LV), VCN in total PBMC and VCN in total BM at Month 12 and busulfan exposure (i.e. total area under the curve [AUC]) during the conditioning phase. • Age at death in the treated subjects compared with the natural history subjects. • Significant (≥ 2 SD) increase of residual ARSA activity compared to pre-treatment values, measured in BM mononuclear cells (MNCs), and peripheral blood (PB) and BM subpopulations at Year 2 after treatment. ARSA activity was also measured in cerebrospinal fluid (CSF) at multiple visits. Secondary safety outcomes: • Absence of immune responses against the transgene (evaluated via immunoassay). • Monitoring of AEs and SAEs, routine laboratory tests, vital signs, physical examinations, specialist examinations, and diagnostic imaging and instrumental tests (including chest x-ray, electrocardiogram and echocardiogram, and echo scan of abdomen and thyroid).

Expanded Access Programmes

CUP 207394

In June 2013, one early-symptomatic EJ patient was treated under a compassionate use scheme as enrolment in Study 201222 was closed to EJ patients. In addition, this patient did not meet the Study 201222 inclusion criterion of ≤ 6 months from onset of symptoms; this patient was symptomatic for 8 months prior to treatment (the protocol for Study 201222 was subsequently amended to increase the sample size and to modify the

inclusion criteria for early-symptomatic EJ subjects to those able to walk for at least 10 steps and normal cognitive function or mild cognitive deterioration with IQ ≥70). No formal inclusion or exclusion criteria were established for this CUP; however, the patient met all the other eligibility criteria defined for Study 201222. The CUP was conducted at the same clinical site and by the same study site staff as Study 201222 and followed the design of Study 201222 where feasible and appropriate. The efficacy endpoints were similar to Study 201222 (see Table C3).

HE 205029

Because Study 201222 was closed for enrolment and no other clinical trials with OTL-200 were open for recruitment, three pre-symptomatic patients were treated under a Hospital Exemption (HE) programme. The enrolment criteria, study design and efficacy endpoints were similar to those defined for Study 201222 (see Table C3).

CUP 206258

Following HE 205029, a new CUP was initiated and five pre-symptomatic patients were treated. The enrolment criteria, study design and efficacy endpoints were similar to those defined for Study 201222 (see Table C3); however the maximum dose was increased from the level specified in the Study 201222 and HE protocols, 20×10^6 cells/kg, to 30×10^6 cells/kg.

Study 205756 (cryopreserved formulation)

Study 205756 is an open-label, single-arm study being conducted in pre-symptomatic subjects with early onset MLD (i.e. either LI, EJ, or an intermediate variant between LI and EJ). (Orchard Data on file, 2019e) This study was initiated in March 2018 to enable continued controlled access to OTL-200 using the intended commercial cryopreserved formulation. Data from the registrational study (Study 201222) informed the design of Study 205756 including subject population, efficacy, and safety endpoints.

After signature of the informed consent, subjects are enrolled in the study. The study comprises four phases, as detailed in section on Study 201222.

Figure C5: Study 205756 design

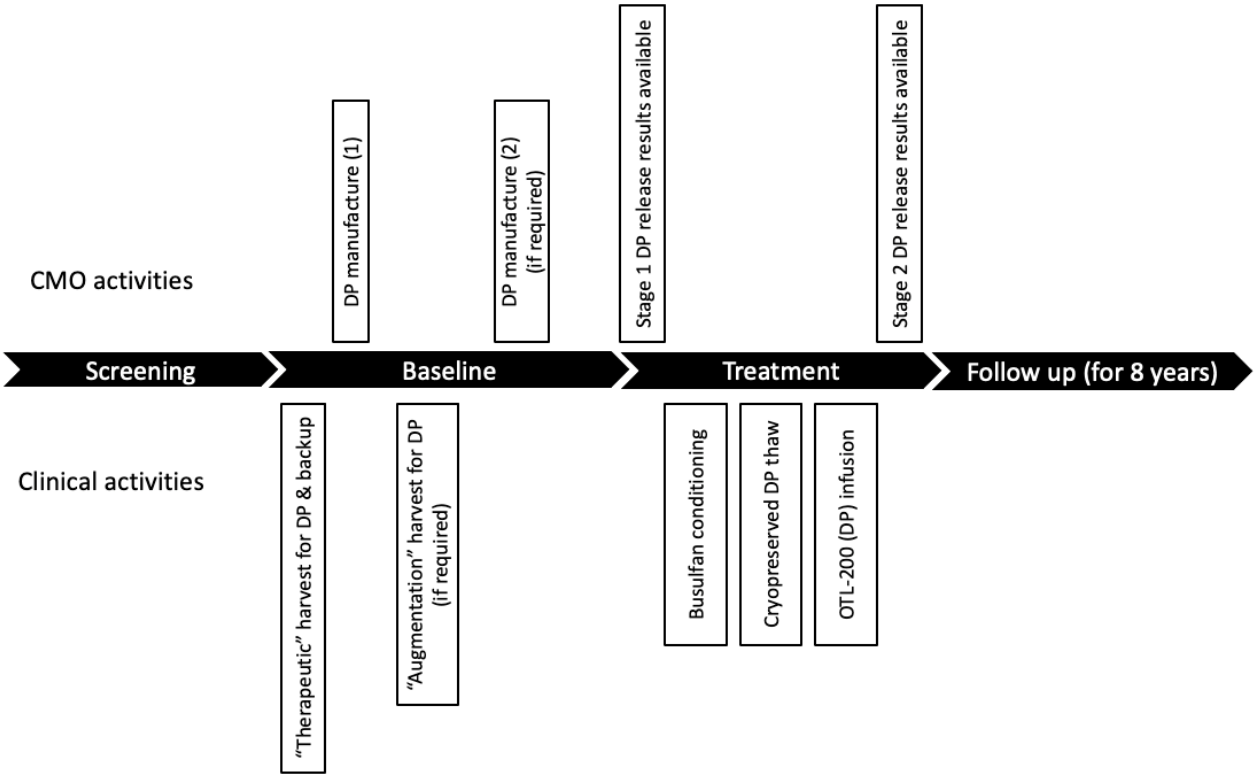


Table C4: Methodology for Study 205756

Study name	Study 205756
Objective	To evaluate the efficacy and safety of the cryopreserved formulation of OTL-200 in up to 10 patients with pre-symptomatic Late Infantile (LI) or Early Juvenile (EJ) metachromatic leukodystrophy (MLD).
Location	Ospedale San Raffaele - Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy.
Design	Non-randomised, open-label, prospective, comparative (non-concurrent control), single-centre study.
Duration of study	Subjects will be followed up for at least 8 years post-treatment.

Patient population	Children up to 6 years of age with early-onset MLD (LI or EJ variants). The LI variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms in the older sibling(s) ≤ 30 months and/or two null (0) mutant ARSA alleles and /or peripheral neuropathy at electroneurographic (ENG) study. The EJ variant was defined by the presence of the following criteria (two out of three criteria were to be met): age at onset of symptoms (in the patient or in the older sibling) between 30 months and 6 years (had not celebrated their 7th birthday), and/or one null (0) and one R mutant ARSA allele(s) and/or peripheral neuropathy at ENG study. Pre-symptomatic clinical status was defined as subjects without neurological impairment (disease- related symptoms), with or without signs of the disease revealed by instrumental evaluations (ENG and brain MRI).
Sample size	N=6 (as of the last data cut); planned total n=10.

Inclusion criteria	Pre-symptomatic MLD subjects with the LI variant or the EJ variant.
	
	Parental/guardian signed and dated informed consent.
	
	The MLD diagnosis was based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles, either known or novel mutations. Novel mutations were analysed with in silico prediction tools and excluded from being known common polymorphisms. In the case of a novel mutation(s), a 24-hour urine collection was required to show elevated sulfatide levels.
	
	Eligible participants must have had EITHER:
	
	• An older sibling affected by MLD (index case), whose age of symptom onset was ≤ 6 years of age (i.e. had not celebrated 7th birthday). Participants were classified as LI, EJ, or intermediate LI/EJ based on age of symptom onset in the index case and their ARSA genotype.
	  ○ LI: symptom onset in the index case ≤ 30 months of age, genotype typically 0/0
	  ○ EJ: symptom onset in index case > 30 months and ≤6 years of age, genotype typically 0/R
	  ○ Intermediate LI/EJ: symptom onset in index case ≤6 years of age but unable to unambiguously characterize index case as LI or EJ
	
	OR
	
	• If MLD was diagnosed in a pre-symptomatic child without an older affected sibling (e.g. incidentally or via newborn screening) and the totality of the available data to the investigator strongly suggested that the subject had an early onset variant of MLD likely to benefit from GT and the subject was ≤6 years of age (i e, had not celebrated 7th birthday), the subject was considered eligible after discussion and approval of the Orchard Therapeutics (Europe) Ltd Medical Monitor (OTL-MM).

Exclusion criteria	Subjects who had symptoms of MLD, defined as EITHER of the following were excluded from study admission: a. Delay in expected achievement of independent standing or independent walking, together with abnormal signs at neurological evaluation b. Documented neurological signs and symptoms of MLD associated with cognitive, motor, or behavioural functional impairment or regression (substantiated by neurological examination and/or neuropsychological tests appropriate for age). Note that seizures and signs of disease revealed at instrumental evaluations (electroneurographic recordings and brain MRI) were not exclusionary if present alone. The appearance of symptoms was reassessed by the responsible physician at or immediately before hospitalisation for therapeutic stem cell harvest and again immediately before commencement of the conditioning regimen in order to confirm treatment eligibility based on absence of disease-related symptoms. In particular, treatment was no longer indicated if the subject had developed the onset of neurological symptoms attributable to disease progression.
Intervention(s) (n = 6) and comparator(s) (n = 0)	Cryopreserved formulation of Libmeldy (OTL-200-c; n=6).
Baseline differences	Not applicable.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	None of the subjects had completed the primary endpoint (defined as completion of 24 months post-treatment) as of the data-cut. The mean follow-up among the 6 subjects was 0.71 year (range: 0.00 to 1.47 year). No subject has withdrawn from the study.
Statistical tests	No formal statistical testing will be performed.
Primary outcomes (including scoring methods and timings of assessments)	Primary efficacy endpoint: GMFM score at 24 months post-gene therapy.

Secondary outcomes (including scoring methods and timings of assessments)	Clinical efficacy: • GMFM score post-gene therapy at multiple visits over time; • Clinical efficacy at 24 months post-gene therapy and multiple visits over time, as measured by: a) Gross Motor Function Classification (GMFC)-MLD score b) Neurological examinations c) Assessment of nerve conduction velocity (NCV) d) Evaluation of brain MRI assessments/parameters (e.g. modified Loes score) e) Neurocognitive assessments Evaluation of engraftment): • %LV positive clonogenic progenitors in bone marrow (BM) at Day 30 post-gene therapy and at multiple visits over time • Vector copy number (VCN) in BM mononuclear cells at Day 30 post-gene therapy and at multiple visits over time • VCN in peripheral blood (PB) mononuclear cells at Day 60 post-gene therapy and at multiple visits over time Pharmacodynamic effect: • The following at Day 60 post-gene therapy and at multiple visits over time: i) ARSA activity in total peripheral blood mononuclear cells (PBMCs) ii) ARSA activity in PB $CD15^+$ cells iii) ARSA activity in PB $CD14^+$ cells • • ARSA activity in cerebrospinal fluid (CSF) at Day 90 post-gene therapy and at multiple visits over time Safety and tolerability: • Safety and tolerability as measured by adverse events (AEs) reporting including: o Conditioning regimen related toxicity and AEs o Non-conditioning related AEs • Haematological recovery, defined as reconstitution of absolute neutrophil count (ANC) > 500 neutrophils/µL, associated with evidence of BM recovery (i.e. no hypocellular marrow) by Day +60 • Incidence and titres of antibodies against ARSA • Absence of malignancy or abnormal clonal proliferation due to insertional oncogenesis • Absence of RCL

Comparator cohort

A non-concurrent comparator group from the OSR-TIGET natural history (NHx) study (n=31) was used for the evaluation of treatment effects in the study analyses. Age and disease variant-matched NHx data were used for comparison purposes. (Orchard Data on file, 2019a)

Among the 31 subjects included as non-concurrent comparator group from the OSR-TIGET NHx study, 19 subjects met the protocol-defined classification for LI MLD and 12 subjects met the protocol-defined classification for EJ MLD.

The limited natural history data in pre-symptomatic or very early symptomatic subjects is justified due to the time from first noticeable symptoms to study enrolment and due to propositions to participate in non-interventional studies being unethical when investigational therapies are available.

In order to minimise the bias linked to differences in age and disease-severity at study entry, in addition to prospective data collection following enrolment in the NHx study, retrospective data available prior to enrolment were also collected with the objective of reconstructing the disease progression of these subjects as much as possible. This approach was applied to the clinical outcomes more amenable to retrospective reconstruction (i.e. gross motor function dynamics using time to acquisition of motor milestones from birth to 18 months of age and Gross Motor Function Classification MLD (GMFC-MLD) from 18 months of age onwards). This strategy enabled a more comprehensive age-matching analysis between the treated and the natural history comparator cohorts.

These untreated matched siblings in the NHx study are particularly appropriate comparators as untreated siblings with the same genotype and family environment are predicted to show very similar disease progression over time. (Mahmood et al., 2010)

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Following discussions with the EMA, data from the registrational Study 201222 and the EAPs were combined to make the Integrated Data Set (IDS; n=29). This approach was deemed acceptable by the EMA considering that comparable protocols, the same drug product formulation, schedule of assessments, and endpoints were used, and the same clinical team were responsible for the enrolment, treatment and follow-up of subjects in the clinical study and EAPs. Due to limited data available at the last data-cut, data from Study 207576 (which uses the cryopreserved formulation) was not included in the IDS.

This submission includes safety data from all 29 patients included in the IDS: 20 from Study 201222 and nine from the EAPs (HE 205029 [n=3], CUP 206258 [n=5] and CUP 207394 [n=1]).

As discussed at the decision problem meeting, this submission presents efficacy data from a post-hoc analysis focussed on the patients within the IDS who fall within the indication. In total [redacted] out of 29 patients in the IDS were included in this analysis:

- [redacted] patients with pre-symptomatic Late Infantile (PS LI) MLD, [redacted] patients with pre-symptomatic Early Juvenile (PS EJ) MLD and [redacted] patients with early-symptomatic Early Juvenile (ES EJ) MLD (hereafter referred to as the Indicated Population, IP).
- The [redacted] patients in the IDS not included in the post hoc efficacy analysis would not be eligible for treatment based on the indication.

In addition, preliminary efficacy and safety data from the six patients treated with the cryopreserved formulation will also be presented in the submission.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

In CUP 206258 the enrolment criteria, study design and efficacy endpoints were similar to those defined for Study 201222 (see Table C3); however the maximum dose was increased from the level specified in the Study 201222 and HE protocols, 20 × 10^6 cells/kg, to 30 × 10^6 cells/kg.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

As agreed in the NICE decision problem meeting and described in Section 9.4.2, the efficacy results presented in this submission are from a post-hoc analysis of data from the patients who fall within the approved indication: [redacted] patients with pre-symptomatic late infantile (PS LI) MLD, [redacted] with pre-symptomatic Early Juvenile (PS EJ) and [redacted] with early-symptomatic Early Juvenile (ES EJ) MLD (i.e. 25 [redacted] of 29 patients treated with OTL-200 fresh formulation). As per the NICE scope, subgroup analyses showing results for each variant according to symptomatic status are also presented. These subgroup analyses were post-hoc.

Figure C6: [redacted]

Note: Four patients in the IDS have been excluded from the post hoc efficacy analysis as they would not meet the criteria for treatment using the refined inclusion criteria for the indication.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Study 201222 (registrational study with fresh formulation, OTL-200-f)

A total of 22 subjects were screened and enrolled into Study 201222. (Orchard Data on file, 2019d) Two of these subjects were withdrawn from the trial prior to treatment. One EJ subject was withdrawn by the investigator at the Baseline visit due to rapid disease progression. A second subject withdrew consent prior to treatment and is not included in any of the datasets presented in this submission.

Figure C7: Subject disposition for Study 201222

EAPs (fresh formulation, OTL-200-f)

A further nine subjects have been treated with OTL-200 following the Study 201222 protocol as part of the EAPs HE 205029 (n=3), CUP 206258 (n=5) and CUP 207394 (n=1). (Orchard Data on file, 2019a) As these studies were either compassionate use or hospital exemption studies, all patients were eligible.

Study 205756 (cryopreserved formulation, OTL-200-c)

As of the data-cut on 14th March 2019, six subjects had been screened for inclusion in this study. (Orchard Data on file, 2019e) One subject was withdrawn by the investigator after the screening visit because whole genome sequencing confirmed that the subject was not affected by MLD; therefore the subject did not meet inclusion criteria. Another subject was withdrawn from the study due to a delay in motor milestones and neurological signs noted during neurological evaluation after Screening, which were exclusion criteria. The remaining four subjects have been treated with the cryopreserved formulation of OTL-200. In addition, at the time of MAA submission (November 2019), two additional patients were enrolled and treated in the study, making a total of six subjects treated with the cryopreserved

formulation of OTL-200. Data from all six patients are included in this submission.

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Study 201222 (registrational study with fresh formulation)

At the time of reporting no subject had completed the study (defined as the completion of the 8-year long-term follow-up visit). Two subjects (both in the EJ group) discontinued study participation due to death attributed to rapid disease progression (at 8 and 15 months post-treatment). Both subjects had onset of cognitive decline or rapid disease progression at the time of treatment. and as such would not have been eligible for treatment as per the proposed indication. (Orchard Data on file, 2019a)

EAPs (fresh formulation)

One EJ subject enrolled in CUP 206258 died due to causes unrelated to OTL-200 treatment or MLD (left hemisphere cerebral ischaemic stroke which occurred 415 days after GT).(Orchard Data on file, 2019a)

Study 205756 (cryopreserved formulation)

At the time of reporting no subject had withdrawn from the study or been lost to follow-up. (Orchard Data on file, 2019e)

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study.

Table C5: Critical appraisal of the non-randomised Study 201222 (registrational study in fresh formulation)

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	The sample selection was appropriate given the rare and rapidly progressing nature of MLD, although not entirely free from potential bias. Patients were evaluated for enrolment using pre-established eligibility criteria, which were designed to balance the potential for clinical benefit with the risks and uncertainties associated with a first-time application of MLD gene therapy in humans. Therefore, the study excluded patients with advanced symptoms and early-symptomatic LIs as they are considered unlikely to obtain clinical benefit from the study drug. The sample size and proportion of pre-symptomatic LI and pre-symptomatic or early-symptomatic EJ patients were revised multiple times during the course of the study with the final design intended to treat a total of 20 patients.
Was the exposure accurately measured to minimise bias?	Yes	As a one-time, single-dose gene therapy, OTL-200 was administered once following stem cell back-up collection, therapeutic bone marrow harvest and busulfan infusion.
Was the outcome accurately measured to minimise bias?	Yes	The outcomes used are validated tools and used to track disease progression in routine clinical practice. Data were collected by the same site staff administering the same tools/assessments, during a similar time-window, and utilising the same instrumentation, methodology, and assessments.
Have the authors identified all important confounding factors?	Yes	The authors identified potential confounding factors of the study such as the disproportionate number of LI patients receiving SMAC and MAC regimens due to their disease subtype and the level of engraftment achieved and underlying motor problems that could affect the results of processing speed scores.

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The authors have performed analyses in populations matched by age at assessment and symptomatic status at baseline. They also addressed the potential confounding factors outlined above, as follows: The goal of increasing the busulfan exposure (i.e. modified, MAC regimen) was to improve the therapeutic potential of OTL-200 on both the CNS and PNS by reducing transduced cell engraftment variability and increasing engraftment levels. Because the therapeutic efficacy of OTL-200 is expected to be related to the proportion of LV-transduced (LV+) HSPC (or their progeny) that stably engraft and/or the average number of integrated ARSA transgenes (VCN) per cell, *in vivo* measurements of engraftment were conducted in each subject at multiple time points post-treatment. • A similar percentage of LV-transduced HSPC (or their progeny) were measured over time in BM after MAC and SMAC, and there was no clear correlation between busulfan exposure and the proportion of LV-positive cells. • Endpoints such as development quotients and age equivalents have been conducted to overcome the limitations observed with the use of IQs and their floor effect in severely impaired MLD patients.
Was the follow-up of patients complete?	No	This submission presents interim results from surviving patients with at least 3 years of follow-up data, following a pre-specified primary analysis performed at 2 years. Patients will be followed up for a protocol-defined 8 years post-treatment.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	The results are presented for each patient and precise central and variance values are provided for descriptive statistics, followed by p values expressed to three digits when comparisons are made.

Table C6: Critical appraisal of the EAPs

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Patients were treated under compassionate use or hospital exemption programmes. Patients were evaluated for enrolment using pre-established eligibility criteria (as for Study 201222), which were designed to balance the potential for clinical benefit with the risks and uncertainties associated with a first-time application of MLD gene therapy in humans. Therefore, the study excluded patients with advanced symptoms and early-symptomatic LIs as they are considered unlikely to obtain clinical benefit from the study drug.
Was the exposure accurately measured to minimise bias?	Yes	As a one-time, single-dose gene therapy, OTL-200 was administered once following stem cell back-up collection, therapeutic bone marrow harvest and busulfan infusion.
Was the outcome accurately measured to minimise bias?	Yes	The outcomes used are validated tools and used to track disease progression in routine clinical practice.
Have the authors identified all important confounding factors?	Yes	The authors identified potential confounding factors of the study such as the level of engraftment achieved and underlying motor problems that could affect the results of processing speed scores.

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The design and analysis of the EAPs match those of Study 201222. Common concerns about possible bias related to variability in operator assessments, or concerns related to the use of historical controls from other sites, are minimized due to this data being collected at the site at which Study 201222 and the EAPs are ongoing, with the same site staff administering tools/assessments, during a similar time-window, and utilizing the same instrumentation, methodology, and assessments that are being employed for bot h the Pivotal 201222 study and the EAPs. The authors have addressed the potential confounding factors, as follows:. Because the therapeutic efficacy of OTL-200 is expected to be related to the proportion of LV-transduced (LV+) HSPC (or their progeny) that stably engraft and/or the average number of integrated ARSA transgenes (VCN) per cell, *in vivo* measurements of engraftment were conducted in each subject at multiple time points post-treatment. Additional analysis of cognitive endpoints such as raw cognitive scores, development quotients and particularly mental age are planned to overcome the limitations observed with the use of IQs and their floor effect in severely impaired MLD patients.
Was the follow-up of patients complete?	No	This submission presents interim results from surviving EAP patients with a range of 1 to 4.5 years follow-up data. Patients will be followed up for a protocol-defined 8 years post-treatment.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	The results are presented for each patient and precise central and variance values are provided for descriptive statistics.

Table C7: Critical appraisal of the non-randomised study 205756 (cryopreserved formulation)

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Study name: Study 205756 (cryopreserved formulation of OTL-200)		
Was the cohort recruited in an acceptable way?	Yes (ongoing)	The sample selection was appropriately designed considering the rarity of the study population. Eligible pre-symptomatic LI and EJ MLD patients must meet appropriate and pre-established inclusion and exclusion criteria.
Was the exposure accurately measured to minimise bias?	Yes	As a one-time, single-dose gene therapy, OTL-200 was administered once following stem cell back-up collection, therapeutic bone marrow harvest and busulfan infusion.
Was the outcome accurately measured to minimise bias?	Yes	The measurements of efficacy and safety of OTL-200 are objective and assess the reconstitution of ARSA activity in the hematopoietic system.
Have the authors identified all important confounding factors?	Yes	The authors identified potential confounding factors of the study, including the possibility of cell loss due to the cryopreservation of OTL-200. The small number of patients enrolled at the time of the 1-year data-cut represent a bias and this has been flagged by the authors.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The study used a wide dose range (i.e. 3–30 × 10^6 $CD34^+$ cells/kg, wider than those ranges used in previous studies) to allow for building in some tolerance for potential cell loss during cryopreservation of the final drug product as well as improved yield based on OTL gene therapy programmes.

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the follow-up of patients complete?	No	This submission presents interim results from six treated patients at <1 year of follow-up. All patients will be followed up for a period of 8 years post-treatment—at the time that OTL-200 becomes approved for commercial use, patients already enrolled into this study may continue to be followed up in an observational long-term follow-up study, as permitted by local regulations. A patient is considered to have completed the primary endpoint if they have completed the follow-up post-treatment visit through the 24-month visit and reported a GMFM score. Due to the short follow-up and small number of subjects enrolled at the time of the data-cut for the results presented in this submission, the limited clinical efficacy data available limit the possibility to determine conclusions on the treatment effects of OTL-200 on clinical efficacy.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	The presented interim results from a small sample size are shown by patient and no comparisons (versus reference values from healthy children) have been made.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem.

9.6.1.1 Study 201222 and EAPs (Integrated Data Set)

Study population

Given the rare nature of MLD and the resulting small number of available study participants, this submission presents data from an integrated analysis of Study 201222 (n=20) and the EAPs (HE 205029 [n=3], CUP 206258 [n=5] and CUP 207394 [n=1]), and data from six patients treated with OTL-200-c, as described in Section 9.4.2.

Figure C8: [redacted]

[redacted]

Table C8: Efficacy outcomes from the indicated population within the IDS (Study 201222 and the EAPs)

Source: (Orchard Data on file, 2019b)

Engraftment				
Durable and stable peripheral engraftment of gene-corrected cells was observed from 1 month post OTL-200 administration in all evaluable subjects, as indicated by: • %LV+ values well above the protocol-defined target of 4% • Persistent VCN in CD34+ cells isolated from the BM and mPB throughout the follow-up period				These biological findings demonstrated a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting microglial reconstitution and the long-term production of ARSA.
Reconstitution of ARSA activity — total PBMC (adjusted mean; nmol/mg/h)				
Subgroup	**Baseline (derived)***	**Year 2**	**Year 3**	**Conclusions**
Late Infantile (pre-symptomatic)	[redacted]	[redacted]	[redacted]	These results provide evidence that genetically modified cells, particularly of the myeloid lineage, effectively migrated to the CNS, engrafted, and produced ARSA enzyme activity within or above the normal range.
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]	[redacted]	
Early Juvenile (early-symptomatic)	[redacted]	[redacted]	[redacted]	

* Values below the LLOQ are imputed with the LLOQ which is [redacted] nmol/mg/h.

GMFM total score compared to age-matched NHx subjects			
Subgroup	**Year 2**	**Year 3**	**Conclusions**
Late Infantile (pre-symptomatic)	[redacted]	[redacted]	Treatment effects observed on gross motor function show a meaningful clinical benefit with OTL-200-treated patients showing normal motor development, stabilisation, or delay in the rate of progression of motor dysfunction compared with untreated age-matched patients.
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]	
Early Juvenile (early-symptomatic)	[redacted]	[redacted]	

GMFC-MLD score compared to all enrolled NHx subjects		
Late Infantile (pre-symptomatic)	[redacted]	Overall GMFC-MLD results were consistent with GMFM results. All OTL-200 treated patients in the indicated population, either stabilised at the same GMFC score throughout the follow-up period or had a slower decline in GMFC score compared to age-matched NHx patients or matched siblings.
Early Juvenile (pre-symptomatic)	[redacted]	
Early Juvenile (early-symptomatic)	[redacted]	

NCV Index compared to age matched NHx data (adjusted mean)			
Subgroup	**Year 2**	**Year 3**	**Conclusions**
Late Infantile (pre-symptomatic)	[redacted]	[redacted]	Results support the benefits of OTL-200 to address demyelination in peripheral nervous system, generally refractory to therapeutic interventions and a major contributor to the gross motor dysfunction in LI and EJ MLD variants.
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]	
Early Juvenile (early-symptomatic)	[redacted]	[redacted]	

Treatment effects on brain MRI (total score)			
Subgroup	**Year 2**	**Year 3**	**Conclusions**
Late Infantile (pre-symptomatic)	[redacted]	[redacted]	These results suggest that treatment with OTL-200 prevents, stabilises, or markedly delays the progressive demyelination and atrophy typically observed as a hallmark of MLD, compared with untreated age-matched patients.
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]	
Early Juvenile (early-symptomatic)	[redacted]	[redacted]	

Overall survival compared to NHx subjects			
Subgroup	**OTL-200**	**NHx**	**Conclusions**
Late Infantile (pre-symptomatic)			These results suggest that treatment with OTL-200 improves overall survival in pre-symptomatic LI MLD compared with untreated patients.
Early Juvenile (pre-symptomatic)			
Early Juvenile (early-symptomatic)			

Overall survival compared to untreated siblings			
Subgroup	**OTL-200**	**NHx**	**Conclusions**
Late Infantile			These results suggest that treatment with OTL-200 improves overall survival in pre-symptomatic LI MLD when compared to untreated siblings.
Early Juvenile			

Severe motor impairment-free survival (sMFS; defined as the interval from birth to the earlier of loss of locomotion and sitting without support [GMFC ≥5] or death from any cause) compared to NHx subjects			
Subgroup	**OTL-200**	**NHx**	**Conclusions**
Late Infantile (pre-symptomatic)			Results from these quality of life-adjusted survival analyses support the fact that subjects treated with OTL-200 show a delay in the time to severe motor impairment (considered end-stage of disease) compared with untreated patients, which is anticipated to reflect in treated subjects and their families/caregivers having better quality of life than their untreated counterparts.
Early Juvenile (pre-symptomatic)			
Early Juvenile (early-symptomatic)			

Severe motor impairment-free survival (sMFS; defined as the interval from birth to the earlier of loss of locomotion and sitting without support [GMFC ≥5] or death from any cause) compared to untreated siblings			
Subgroup	**OTL-200**	**NHx**	**Conclusions**
Late Infantile			These results support the fact that subjects treated with OTL-200 show a delay in the time to severe motor impairment (considered end-stage of disease) compared with matched untreated siblings, which is anticipated to reflect in treated subjects and their families/caregivers having better quality of life than their untreated counterparts.
Early Juvenile			

Severe cognitive and motor impairment-free survival (sCMFS; defined as the interval from birth to severe cognitive impairment [DQp ≤55] and loss of locomotion and sitting without support [GMFC ≥5] or death from any cause) compared to NHx subjects			
Subgroup	**OTL-200**	**NHx**	**Conclusions**
Late Infantile (pre-symptomatic)			These results support the fact that subjects treated with OTL-200 show a delay in the time to severe cognitive and motor impairment (considered end-stage) compared with untreated patients, which is anticipated to reflect in treated subjects and their families/caregivers having better quality of life than their untreated counterparts.
Early Juvenile (pre-symptomatic)			
Early Juvenile (early-symptomatic)			

Severe cognitive and severe motor impairment-free survival (sCMFS; defined as the interval from birth to severe cognitive impairment [DQp ≤55] and loss of locomotion and sitting without support [GMFC ≥5] or death from any cause) compared to untreated siblings			
Subgroup	**OTL-200**	**NHx**	**Conclusions**
Late Infantile			These results support the fact that subjects treated with OTL-200 show a delay in the time to severe cognitive and motor impairment (considered end-stage) compared with matched untreated siblings, which is anticipated to reflect in treated subjects and their families/caregivers having better quality of life than their untreated counterparts.
Early Juvenile			

Development quotient (adjusted mean score)			
Subgroup	**Year 2**	**Year 3**	**Conclusions**
Late Infantile (pre-symptomatic)			These results support the positive treatment effects of OTL-200 on cognitive function and provide further evidence of the benefit of OTL-200 to treat the key clinical manifestations of MLD.
Early Juvenile (pre-symptomatic)			
Early Juvenile (early-symptomatic)			

* Baseline (derived) is equal to a subject's result at the Baseline visit, if present. If a subject did not have a Baseline visit, data from the Screening visit was used.

Engraftment

The therapeutic efficacy of OTL-200 is expected to occur when sufficient gene-corrected (LV transduced (LV+) haematopoietic stem and progenitor cells (HSPC) or their progeny stably engraft, and there is a sufficient number of integrated ARSA transgenes (VCN) per cell. Therefore *in vivo* measurements of these parameters were conducted in each subject at multiple time points post-GT. (Orchard Data on file, 2019a)

LV+ transduced cell engraftment above 4% in BM-derived clonogenic progenitor cells at Year 1 after treatment was a secondary endpoint for this development programme. The 4% threshold was chosen based on clinical experience in other gene therapy trials, which have demonstrated 4% average long-term engraftment of autologous hematopoietic stem/progenitor cells transduced with gamma-retroviral vectors in the bone marrow of paediatric subjects suffering from adenosine deaminase severe combined immunodeficiency (ADA-SCID) and receiving reduced intensity, nonmyeloablative conditioning (Aiuti et al., 2009, Aiuti et al., 2002).

Durable and stable peripheral engraftment of gene-corrected cells was observed from 1 month post OTL-200 administration in all evaluable subjects, as indicated by %LV+ values well above the protocol-defined target of 4% and persistent VCN in CD34+ cells isolated from the BM and PB throughout the follow-up period. These biological findings demonstrated a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting microglial reconstitution and the long-term production of ARSA. (Orchard Data on file, 2019b)

Figure C9: [redacted]

Note: Geometric means and 95% confidence intervals are presented where there are at least three subjects with non-missing data.

Figure C10: [redacted]

Note: Values = 0 are plotted at 0.001.
Note: LOQ is [redacted] VCN/cell. Values < LOQ are imputed at LOQ. Geometric means and 95% confidence intervals are presented where there are at least three subjects with non-missing data.

Engraftment was consistently observed across PS LI, PS EJ and ES EJ MLD variants and across the age range of treated subjects, suggesting no impact of chronological age on the achievement of sustained levels of engraftment. (Orchard Data on file, 2019a)

Reconstitution of ARSA activity

A co-primary efficacy endpoint for Study 201222 and the EAPs was to demonstrate a statistically significant increase in residual ARSA activity in PBMCs at Year 2 post-treatment as compared to pre-treatment values.

Measurement of the reconstitution of ARSA activity in the haematopoietic system was performed on PBMCs, BM mononuclear cells, and other PB and BM subpopulations. ARSA activity in CSF was also quantified to provide indirect evidence that transduced cells have migrated to the central nervous system (CNS) and are producing and secreting functional ARSA enzyme. (Orchard Data on file, 2019a)

Table C9: Reconstitution of ARSA activity — total PBMC (adjusted mean; nmol/mg/h)

Subgroup	Baseline (derived)*	Year 2	Year 3
Late Infantile (pre-symptomatic)	[redacted]	[redacted]	[redacted]
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]	[redacted]
Early Juvenile (early-symptomatic)	[redacted]	[redacted]	[redacted]

* Values below the LLOQ are imputed with the LLOQ which is [redacted] nmol/mg/h.

[redacted] (see Figure C11).

(Orchard Data on file, 2019a)

Figure C11: [redacted]

Note: Values < LLQ are imputed at LLQ. LLQ is [redacted] nmol/mg/h. GMs and 95% CIs are presented where there are at least three subjects with non-missing data.
ARSA: arylsulfatase A; CI: confidence interval; GM: geometric mean; LLQ: lower limit of quantification; PBMCs: peripheral blood mononuclear cells.

[redacted]

Figure C12: [redacted]

Note: Values < LLQ are imputed at LLQ. LLQ is [redacted] nmol/mg/h. GMs and 95% CIs are presented where there are at least three subjects with non-missing data.
ARSA: arylsulfatase A; CI: confidence interval; GM: geometric mean; LLQ: lower limit of quantification.

These results provide indirect evidence that genetically modified cells, particularly of the myeloid lineage, effectively migrated to the CNS, engrafted, and produced ARSA enzyme activity within or above the normal range. For subjects with undetectable levels of ARSA activity, the assay lower limit of quantification was imputed as this represents a conservative approach for the evaluation of treatment effects in those cases.

Treatment effect on gross motor function

LI and EJ variants of MLD are characterised by rapid decline in gross motor function. Stability or reduced progression of clinical motor impairment compared to the NHx course of the disease is therefore considered to be a clinically relevant benefit to patients and their families.

Two motor function measures were used in the OTL-200 clinical development programme to evaluate treatment effects on motor function: GMFM total score and GMFC-MLD. (Orchard Data on file, 2019a)

GMFM total score

The GMFM score is related to age, and by the age of 60 months most healthy children will achieve their maximum score, approximating 100%. In contrast, children with LI MLD, who typically have overt symptom onset by <30 months of age, show a progressive decline in motor function, are bedridden within 2 to 3 years after disease onset, and show GMFM scores reported to be <2% of the total score obtained by a healthy child older than 50 months (Biffi et al., 2008).

An improvement greater than 10% in the GMFM total score of subjects treated with OTL-200 when compared to GMFM total scores in the age matched untreated MLD subjects evaluated at Year 2 after treatment was a coprimary endpoint for Study 201222 and the EAPs. GMFM is a clinically relevant endpoint, being a direct measure of motor impairment. According to medical experience, an improvement of the 10% of the maximum value (best score 264 = improvement of 26.4 points) of the scale of a patient's score corresponds to a significant improvement in the quality of life of the subject.

Subjects in the indicated population (PS LI, PS EJ and ES EJ MLD) showed normal motor development, or stabilisation or delay in the rate of progression of motor dysfunction as measured by lower GMFM total scores (%) compared with age-matched untreated patients. (Orchard Data on file, 2019a)

Figure C13: [redacted]

LS means and difference were from an ANCOVA analysis, adjusted for age and treatment.
OSR-TIGET NHx Study subjects were age and disease subtype matched to the OTL-200-treated subjects.
Data were not available for CUP 206258 patients because they were not yet followed to Year 2 at the time of the data cut-off for the integrated analyses.
Source: Data on file

Figure C14: [redacted]

LS means and difference were from an ANCOVA analysis, adjusted for age and treatment.
OSR-TIGET NHx Study subjects were age and disease subtype matched to the OTL-200-treated subjects.
Data were not available for CUP 206258 patients because they were not yet followed to Year 2 at the time of the data cut-off for the integrated analyses.
Source: Data on file

Figure C15: [redacted]

LS means and difference were from an ANCOVA analysis, adjusted for age and treatment.
OSR-TIGET NHx Study subjects were age and disease subtype matched to the OTL-200-treated subjects.
Data were not available for CUP 206258 patients because they were not yet followed to Year 2 at the time of the data cut-off for the integrated analyses.
Source: Data on file

GMFC-MLD score

In addition to the analyses of GMFM scores, treatment effects of OTL-200 on gross motor function were assessed by the use of GMFC-MLD. (Orchard Data on file, 2019a)

The GMFC-MLD provides a standardized assessment of all clinically relevant stages from normal (GMFC-MLD Level 0) to loss of all gross motor function (GMFC-MLD Level 6). However, this assessment can only be carried out from the age of 18 months onwards.

Table C10: Levels of GFMC in MLD

Level	Description
0	Walking without support with quality of performance normal for age
1	Walking without support but with reduced quality of performance, i.e., instability when standing or walking
2	Walking with support. Walking without support not possible (fewer than five steps)
3	Sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible
4	(a) Sitting without support but no locomotion, or (b) Sitting without support not possible, but locomotion such as crawling or rolling
5	No locomotion nor sitting without support, but head control is possible
6	Loss of any locomotion as well as loss of any head and trunk control

Overall, the gross motor function results assessed by the GMFC-MLD were consistent with results measured with the GMFM, in the PS LI, PS EJ and ES EJ subgroups in the indicated population. (Orchard Data on file, 2019b)

[redacted]

Figure C16: [redacted]

Abbreviations: Pre-Symp=pre-symptomatic at GT
Notes: The boxplots display the 10th, 25th 50th, 75th, and 90th percentiles. Untreated sibling data is a subset of the NHx data.

[redacted]

[redacted]

[redacted](Orchard Data on file, 2019d)

In contrast, data from both the age-matched NHx subjects and published data (Kehrer et al., 2011b) show that untreated subjects followed a rapid trajectory of deterioration.

Figure C17: [redacted]

Abbreviations: Pre-Symp=pre-symptomatic at GT; Symp=symptomatic at GT
Notes: The boxplots display the 10th, 25th 50th, 75th, and 90th percentiles. Untreated sibling data is a subset of the NHx data.

Treatment effects on cognitive function

The development, stability, or regression of a subject's cognitive abilities were monitored using neuropsychological tests administered according to the chronological age and cognitive status of the subject. (Orchard Data on file, 2019a)

Historically, the use of IQ scores for analysis of cognitive function has been preferred to age equivalent scores or developmental quotient as the latter do not take into account the normal range. However, IQ scores reach a floor

effect for an IQ < 40, below which cognitively impaired children cannot be evaluated reliably, reducing the sensitivity for monitoring cognitive function over time.

In order to uncover the degree of cognitive impairment extending beneath the floor effect of 40 in treated and NHx subjects, age equivalent and developmental quotient (DQ) were used as exploratory analyses of cognitive function in Study 201222 and the EAPs. (Orchard Data on file, 2019a)

Table C11: Development quotient (adjusted mean score)

Subgroup	Year 2	Year 3
Late Infantile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (early-symptomatic)	[redacted]	[redacted]

[redacted]

Figure C18: [redacted]

Notes: DQ (Performance) at each visit is based on the performance and perceptual reasoning scales for WPPSI and WISC respectively. For Bayley II/III and in cases where a neuropsychological assessment has been performed but a questionnaire could not be completed due to severe clinical condition of the patient, DQP at each visit is based on (Cognitive Age-Equivalent/Chronological Age) x 100. Reference lines represent cut-offs for degree of Cognitive Impairment: <=55 (Severe Cognitive Impairment), >55- <70 (Moderate Cognitive Impairment), >=70-<85 (Mild Cognitive Impairment), >=85 (Normal).

[redacted]

Figure C19: [redacted]

Notes: DQ (Performance) at each visit is based on the performance and perceptual reasoning scales for WPPSI and WISC respectively. For Bayley II/III and in cases where a neuropsychological assessment has been performed but a questionnaire could not be completed due to severe clinical condition of the patient, DQP at each visit is based on (Cognitive Age-Equivalent/Chronological Age) x 100. Reference lines represent cut-offs for degree of Cognitive Impairment: <=55 (Severe Cognitive Impairment), >55- <70 (Moderate Cognitive Impairment), >=70-<85 (Mild Cognitive Impairment), >=85 (Normal).

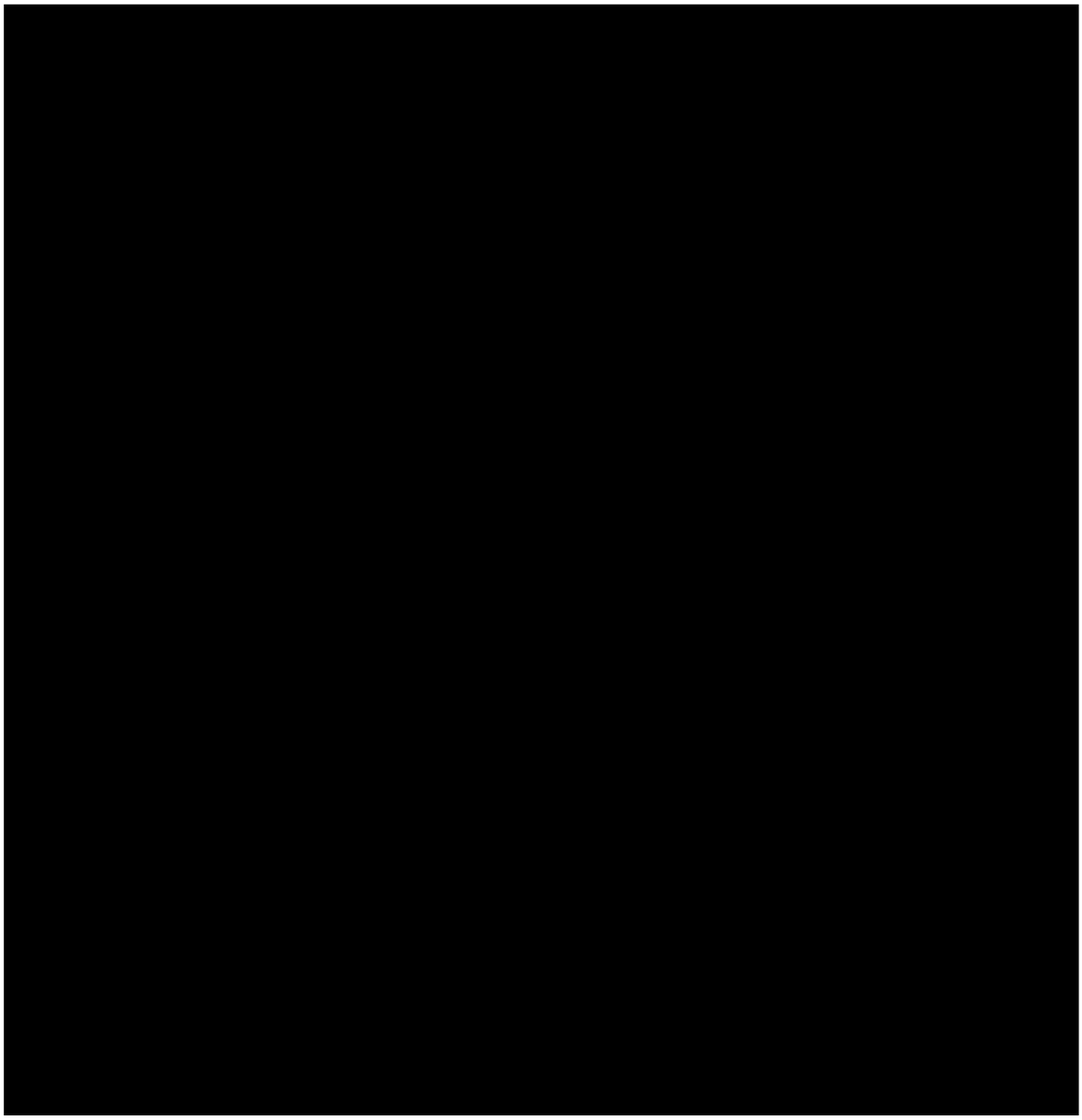
[redacted]

Figure C20: [redacted]

Notes: DQ (Performance) at each visit is based on the performance and perceptual reasoning scales for WPPSI and WISC respectively. For Bayley II/III and in cases where a neuropsychological assessment has been performed but a questionnaire could not be completed due to severe clinical condition of the patient, DQP at each visit is based on (Cognitive Age-Equivalent/Chronological Age) x 100. Reference lines represent cut-offs for degree of Cognitive Impairment: <=55 (Severe Cognitive Impairment), >55- <70 (Moderate Cognitive Impairment), >=70-<85 (Mild Cognitive Impairment), >=85 (Normal).

Age-equivalent scores showed normal acquisition of cognitive skills in the majority of treated PS LI, PS EJ and ES EJ subjects at chronological ages at which untreated NHx subjects showed severe cognitive impairment. In the small number of subjects who showed cognitive development below the normal range or declined years after GT, scores were better than NHx subjects at comparable chronological ages. (Orchard Data on file, 2019a)

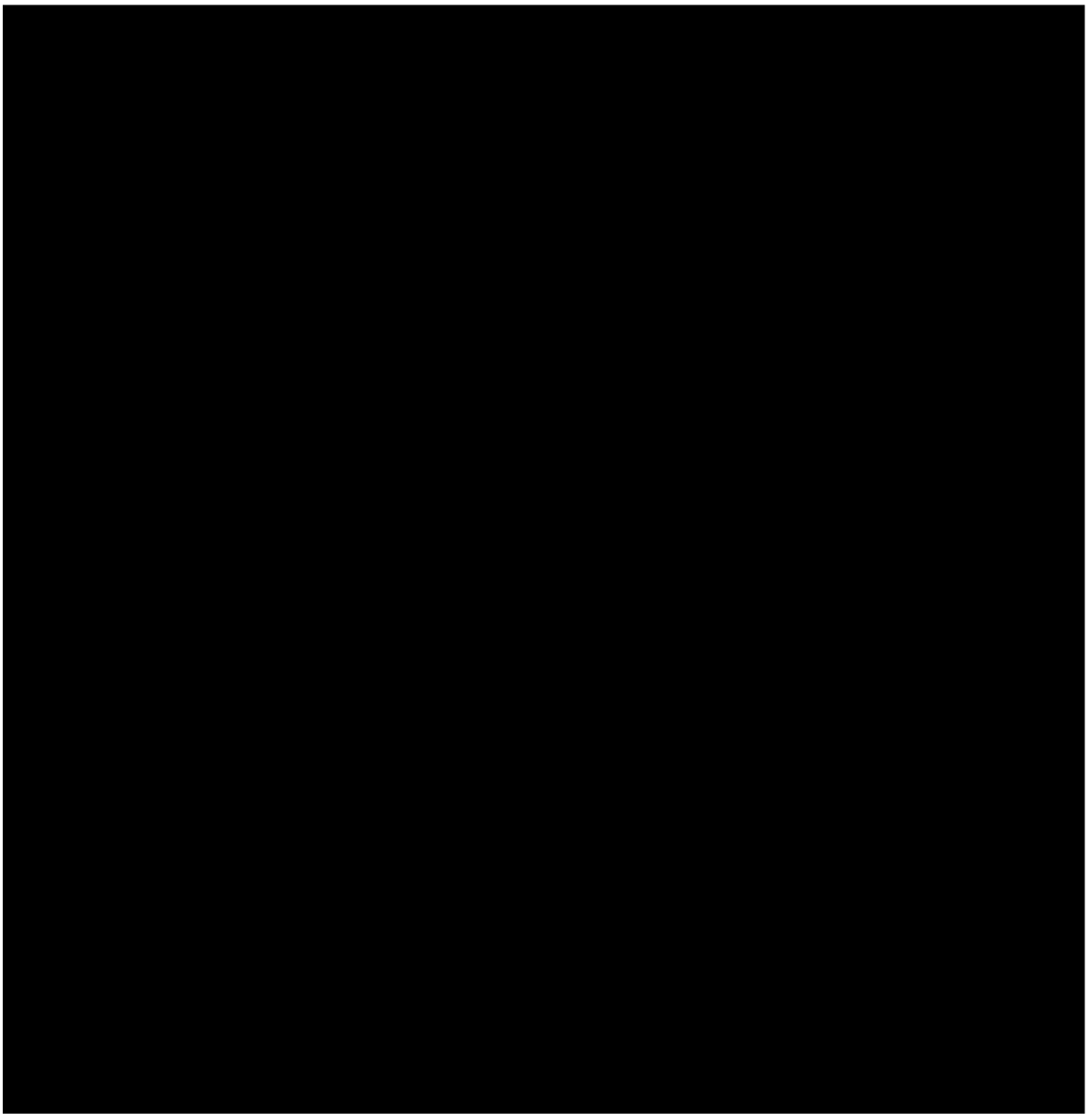
Figure C21: [redacted]



Notes: Cognitive Age-Equivalent at each visit has been derived as follows: For WPPSI and WISC: (DQp x Chronological Age)/100. For Bayley III: Cognitive Raw Scores have been compared to the tabulated values in the Bayley III manual to calculate Cognitive Age-Equivalent. For Bayley II and in cases where a neuropsychological assessment has been performed but a questionnaire could not be completed due to severe clinical condition, Cognitive Age-Equivalent is based on Mental Development Age as reported on the CRF.

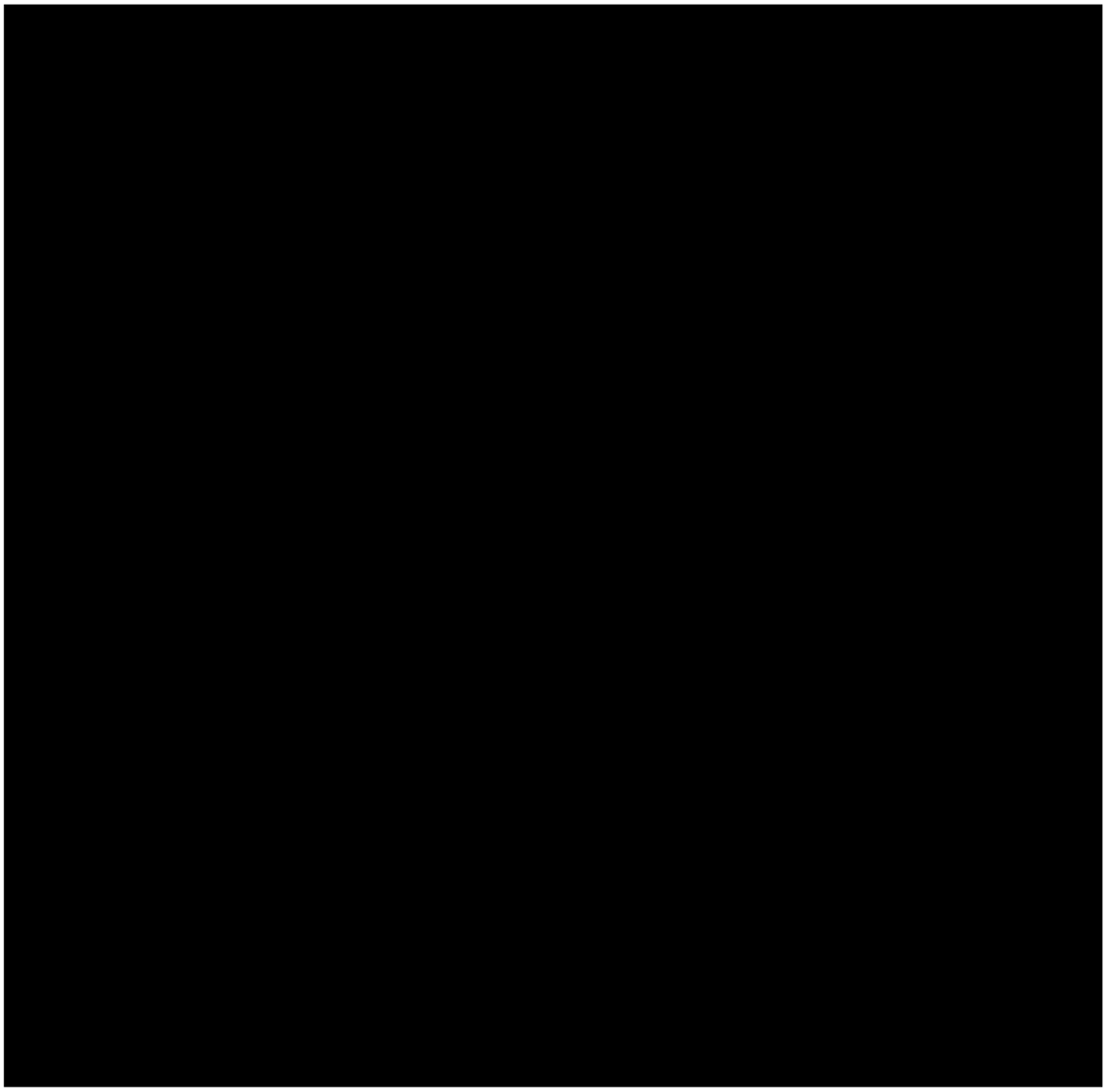
Bayley N. Bayley scales of infant and Toddler Development. Third Edition, 2006.

Figure C22: [redacted]



Notes: Cognitive Age-Equivalent at each visit has been derived as follows: For WPPSI and WISC: (DQp x Chronological Age)/100. For Bayley III: Cognitive Raw Scores have been compared to the tabulated values in the Bayley III manual to calculate Cognitive Age-Equivalent. For Bayley II and in cases where a neuropsychological assessment has been performed but a questionnaire could not be completed due to severe clinical condition, Cognitive Age-Equivalent is based on Mental Development Age as reported on the CRF.
Bayley N. Bayley scales of infant and Toddler Development. Third Edition, 2006.

Figure C23: [redacted]



Notes: Cognitive Age-Equivalent at each visit has been derived as follows: For WPPSI and WISC: (DQp x Chronological Age)/100. For Bayley III: Cognitive Raw Scores have been compared to the tabulated values in the Bayley III manual to calculate Cognitive Age-Equivalent. For Bayley II and in cases where a neuropsychological assessment has been performed but a questionnaire could not be completed due to severe clinical condition, Cognitive Age-Equivalent is based on Mental Development Age as reported on the CRF. Bayley N. Bayley scales of infant and Toddler Development. Third Edition, 2006.

These results support the positive treatment effects of OTL-200 and provide further evidence of the benefit of its effect in treating the key clinical manifestations of MLD.

Treatment effects on brain MRI

The effect of OTL-200 on the progression of white matter demyelination and atrophy in the CNS was assessed using brain MRI, performed and interpreted at a single institution by an independent neuroradiologist. Quantification of MRI abnormalities was performed by adapting and optimizing the Loes' scoring system previously used for adrenoleukodystrophy and MLD (Biffi et al., 2008, Loes et al., 1994, Sessa et al., 2016b). The adapted MRI score ranges from 0 (normal) to 31.5 (markedly abnormal), and a score of > 0 is considered abnormal. The same imaging methodology was used for subjects treated in Study 201222, EAPs and those participating in the NHx study, therefore minimizing the potential inter- and intra-site variability in results. (Orchard Data on file, 2019b)

Table C12: Treatment effects on brain MRI (total score)

Subgroup	Year 2	Year 3
Late Infantile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (early-symptomatic)	[redacted]	[redacted]

[redacted]

[redacted] (Orchard Data on file, 2019b)

[redacted]

Figure C24: [redacted]

Figure C25: [redacted]

Figure C26: [redacted]

These results suggest that treatment with OTL-200 prevents, stabilises, or markedly delays the progressive demyelination and atrophy typically observed as a hallmark of MLD, compared with age-matched untreated subjects.

These treatment effects of OTL-200 on brain demyelination and atrophy are consistent with the treatment effect observed on motor function and cognition and expand on the mechanism of action of OTL-200 to address the common disease pathophysiology across MLD variants translating into relevant clinical benefits.

Treatment effects on peripheral nervous system

Peripheral neuropathy, characterised by severe slowing of motor and sensory nerve conduction, often precedes the CNS manifestations of MLD, particularly in LI MLD (Bindu et al., 2005, Dali et al., 2015, Miller, 1985, Zafeiriou et al., 1999) and contributes to the gross motor impairment observed in this MLD variant.

The efficacy of OTL-200 in stabilising or reducing the progression of the disease in the PNS was evaluated using nerve conduction velocity (NCV) from electroneurography ENG recordings and interpreted at a single institution by the same neurophysiologist. (Orchard Data on file, 2019b)

Table C13: NCV Index compared to NHx data (adjusted mean)

Subgroup	Year 2	Year 3
Late Infantile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (early-symptomatic)	[redacted]	[redacted]

[redacted]

[redacted] (Biffi et al., 2008).

Overall, the treatment effects on peripheral neuropathy in PS LI subjects can be regarded as clinically relevant, particularly considering that most subjects enrolled already had signs of PNS impairment at the time of treatment.

Treatment effects on peripheral neuropathy support the benefits of OTL-200 to address demyelination in the peripheral nervous system, generally refractory to therapeutic interventions and a major contributor to the gross motor dysfunction in early onset MLD variants.

Figure C27: [redacted]

Analysis visit is the visit from the OTL-200-f subjects used in the ANCOVA analysis. Subjects from the natural history arm are age and disease subtype matched to the OTL-200-f arm. Note: Least square (LS) means and difference from analysis using an ANCOVA adjusted for age and treatment.

Figure C28: [redacted]

Analysis visit is the visit from the OTL-200-f subjects used in the ANCOVA analysis. Subjects from the natural history arm are age and disease subtype matched to the OTL-200-f arm. Note: Least square (LS) means and difference from analysis using an ANCOVA adjusted for age and treatment.

Figure C29: [redacted]

Analysis visit is the visit from the OTL-200-f subjects used in the ANCOVA analysis. Subjects from the natural history arm are age and disease subtype matched to the OTL-200-f arm. Note: Least square (LS) means and difference from analysis using an ANCOVA adjusted for age and treatment**.**

Overall survival

Table C14: Overall survival compared to NHx subjects

Subgroup	OTL-200	NHx
Late Infantile (pre-symptomatic)		
Early Juvenile (pre-symptomatic)		
Early Juvenile (early-symptomatic)		

* One PS EJ subject died of cerebral ischaemic infarction unrelated to OTL-200 treatment.

Table C15: Overall survival compared to untreated siblings

Subgroup	OTL-200	NHx
Late Infantile		
Early Juvenile		

[redacted]

[redacted] (Orchard Data on file, 2019b) [redacted]

[redacted]

Figure C30: [redacted]

Note: The age at death (overall survival - OS) is defined as the interval from birth to the event of death from any cause; otherwise OS is censored at the last contact date up to and including the respective study data cut-off date. Symptomatic status refers to OTL-200 treated subjects at time of treatment. Natural history patients also presented.

Figure C31: [redacted]

Note: The age at death (overall survival - OS) is defined as the interval from birth to the event of death from any cause; otherwise OS is censored at the last contact date up to and including the respective study data cut-off date. Symptomatic status refers to OTL-200 treated

subjects at time of treatment. Natural history patients also presented.

Figure C32: [redacted]

Note: The age at death (overall survival - OS) is defined as the interval from birth to the event of death from any cause; otherwise OS is censored at the last contact date up to and including the respective study data cut-off date.Symptomatic status refers to OTL-200 treated subjects at time of treatment. Natural history patients also presented.

Composite quality of life-adjusted survival endpoints

Given the advances in supportive care, patients are now able to survive for many years in an advanced stage of the disease with supportive care (Mahmood et al., 2010). Because overall survival results may be confounded by different approaches of families and health system to receiving supportive care whilst in the advanced stages of disease, quality-adjusted survival analyses were conducted. These analyses involved the comparison of composite endpoints of time to severe motor impairment or death and time to severe cognitive and motor impairment or death in treated subjects with the NHx population.

The tables (Table C15 and Table C16) and figures (Figure C33 and Figure C34) below represent the time to severe motor impairment-free survival. Severe motor impairment-free survival (sMFS) was defined as the interval

from birth to loss of locomotion and loss of sitting without support (GMFC Level 5 or higher) or death. Data from NHx subjects for Level 5 or higher were available and compared to treated subjects; treated subjects were also compared to matched siblings where possible. [redacted] (Orchard Data on file, 2019b)

Table C16: Severe motor impairment-free survival (sMFS) compared to NHx subjects

Subgroup	OTL-200	NHx
Late Infantile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (pre-symptomatic)	[redacted]	[redacted]
Early Juvenile (early-symptomatic)	[redacted]	[redacted]

Table C17: Severe motor impairment-free survival (sMFS) compared to matched siblings

Subgroup	OTL-200	NHx
Late Infantile	[redacted]	[redacted]
Early Juvenile	[redacted]	[redacted]

[redacted]

Figure C33: [redacted]

[redacted]

[redacted]

Figure C34: [redacted]

[redacted]

Figure C35: [redacted]

[redacted]

Figure C36: [redacted]

Severe cognitive and motor impairment-free survival (sCMFS) is defined as the interval from birth to severe cognitive impairment (DQ Performance ≤55) and loss of locomotion and loss of sitting without support (GMFC Level 5 or higher) or death from any cause.

Table C18: Severe cognitive and motor impairment-free survival (sCMFS) compared to NHx subjects

Subgroup	OTL-200	NHx
Late Infantile (pre-symptomatic)		
Early Juvenile (pre-symptomatic)		
Early Juvenile (early-symptomatic)		

Table C19: Severe cognitive and motor impairment-free survival (sCMFS) compared to untreated siblings

Subgroup	OTL-200	NHx
Late Infantile	[redacted]	[redacted]
Early Juvenile	[redacted]	[redacted]

[redacted]

Figure C37: [redacted]

[redacted]

[redacted]

Figure C38: [redacted]

[redacted]

Figure C39: [redacted]

[redacted]

Figure C40: [redacted]

[redacted]

Results from these quality of life-adjusted survival analyses support the fact that subjects treated with OTL-200 experience a delay in the time to severe motor impairment and cognitive impairment or death.

9.6.1.2 Study 205756 — cryopreserved formulation

Study population

Preliminary clinical data from Study 205756 support the *in vitro* analytical comparability and *in vivo* comparability data between the fresh and cryopreserved formulation of OTL-200. (Orchard Data on file, 2019a)

Preliminary data are available from six patients treated with the cryopreserved formulation of OTL-200 (as at MAA submission in November 2019). (Orchard Data on file) None of the subjects had reached the time point for the primary endpoint (24 months post treatment). [redacted]

Table C20: Patient details for Study 205756

	Patient 1 MLDCRY02	Patient 2 MLDCRY03	Patient 3 MLDCRY04	Patient 4 MLDCRY06	Patient 5 MLDCRY08	Patient 6 MLDCRY09
MLD variant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic status at time of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at OTL-200 administration (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study duration (study visit completed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table C21: Preliminary outcomes from Study 205756: Evaluation of efficacy

	Patient 1, LI variant	Patient 2, LI variant	Patient 3, EJ variant	Patient 4, EJ variant	Patient 5, EJ variant	Patient 6, LI variant
Percent lentiviral vector transduced cells after administration of OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VCN in total MNC in bone marrow after administration of OTL-200-c (VCN/cell)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARSA activity in PBMCs (Baseline and most recent measurement; nmol/mg/h)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFM scores	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Patient 1, LI variant	Patient 2, LI variant	Patient 3, EJ variant	Patient 4, EJ variant	Patient 5, EJ variant	Patient 6, LI variant
Brain MRI total scores	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* ARSA activity in total PBMCs was not measured at Baseline for Patient 1 due to insufficient material (protocol deviations). The Screening level for Patient 4 was [redacted] nmol/mg/h and is provided in this table as the Baseline value.

Engraftment

The therapeutic efficacy of OTL-200 is expected to occur when sufficient gene-corrected (LV transduced (LV^+) haematopoietic stem and progenitor cells (HSPC) or their progeny stably engraft, and there is sufficient number of integrated ARSA transgenes (VCN) per cell. Therefore *in vivo* measurements of these parameters were conducted in each subject at multiple time points post-GT.

The percentage of LV^+ clonogenic progenitors in BM at Day 30 post-treatment and at multiple visits over time was a secondary endpoint of this study. Colony-forming unit assays were performed on BM-derived cells at multiple time points over the course of follow-up after administration of OTL-200. Results are expressed as a percentage (%) of LV^+ colonies among the total (erythroid and myeloid) tested colonies.

[redacted]

It should be noted that the cryopreserved formulation of OTL-200 shows similar engraftment characteristics to the fresh formulation at the same timepoints. This clinical experience with the fresh product gives confidence that cryopreserved formulation will achieve the expected clinical milestones and benefits seen with the fresh formulation.

Reconstitution of ARSA activity

[redacted]

GMFM scores

[redacted] (Palisano et al., 1997)

Figure C41: [redacted]

Abbreviation: GMFM: Gross Motor Function Measure
Note: Vertical dotted lines represent expected age of disease onset.

MRI total scores

Given the number of subjects and limited duration of follow-up there were limited data available from MRI assessments, [redacted]

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

All analyses were performed on data from the ITT population.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The studies presenting rates of adverse events with OTL-200 have been identified as described in Section 9.1 to Section 9.6. In order to provide a comprehensive overview of the safety of OTL-200, the safety data presented in this section are from an integrated analysis of the data from all 29 patients (the IDS) included in the studies previously outlined in Table C2. These patients had been treated with the fresh formulation of OTL-200 under the protocol for the registrational study (201222; n=20) and EAPs (n=9). (Orchard Data on file, 2019c)

Preliminary safety data are also presented for the cryopreserved formulation of OTL-200 (Study 205756). (Orchard Data on file, 2019e)

9.7.2 Provide details of all important adverse events reported for each study.

9.7.2.1 Study 201222 and EAPs (IDS)

In general, OTL-200 appears to have been well-tolerated with no treatment-related mortality or treatment-related SAEs. (Orchard Data on file, 2019c)

Table C22: Adverse events across patient groups

	Integrated data set (n=29)
	OTL-200, n (%)
Any serious adverse events	20 (69)
Most common Grade 3 adverse event attributed to busulfan	
Febrile neutropenia	23 (79)
Stomatitis	12 (41)
Mucosal inflammation	9 (31)
Veno-occlusive disease	3 (10)
Adverse events associated with the background disease (MLD)	
Gait disturbance	15 (52)
Motor dysfunction	9 (31)
Muscle spasticity	9 (31)
Aphasia	6 (21)
Ataxia	5 (17)
Dysarthria	5 (17)
Cognitive disorder	4 (14)
Dysphagia	4 (14)
Seizure	2 (7)
Renal tubular acidosis	
Event in pre-treatment period	8 (28)
Event during treatment period	4 (14)
Event at 3 months post-treatment	2 (7)

CI, confidence interval
Adapted from European Public Assessment Reports published by the European Medicines Agency

All 29 subjects in the IDS experienced at least one AE (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade of 3) after OTL-200 treatment. The most frequently reported Grade 3 AEs (>50% of subjects) were febrile neutropenia (79% of subjects), gait disturbance (52% of subjects), and stomatitis (41% of subjects) (Table C10).

None of the SAEs were considered by the investigator to be related to OTL-200 but were mainly related to myeloablative conditioning with busulfan and to the background disease. All subjects demonstrated good haematological recovery after busulfan conditioning and there were no unexpected short-to-medium term safety signals associated with the conditioning regimen or with the infusion of transduced cells.

Three SAEs with a fatal outcome were reported in the IDS but all were deemed unrelated to OTL-200. In particular, two deaths were attributed to rapid MLD disease progression and occurred in patients who would not be eligible for treatment in the post-market authorisation settings given the approved indication. The other death which occurred 415 days after gene therapy, was attributed to left hemisphere cerebral ischemic stroke and deemed by the investigator to be unrelated to OTL-200. No meaningful differences were observed in the safety profile of OTL-200 for the two early-onset MLD variants (LI and EJ).

Four subjects reported an AE of Grade 2 anti-ARSA antibodies (AAA; preferred term [PT] ‘antibody test positive’) which resolved spontaneously (one subject) or after a short treatment with rituximab (three subjects). The AAA titres were generally low. There was no evidence of a negative clinical effect observed on ARSA activity in PBMCs (or any other relevant cellular subpopulations) nor in the ARSA activity in CSF in any of the subjects reporting positive AAA. Moreover, there were no reports of apparent AE trends in subjects with positive compared to the those who did not test positive.

To date, no cases of malignancy or AEs indicative of oncogenic transformation have been reported and there is no evidence of aberrant clonal proliferation based on insertion site analysis. Potential risk of RCL was also

monitored in all treated subjects and the totality of the clinical data have revealed no evidence of development of RCL.

Overall, the safety findings following treatment with OTL-200 are consistent with what would be expected in patients with MLD and who have undergone busulfan conditioning and subsequent haematological reconstitution.

The following sections will provide a summary of the most common AEs reported in clinical development with the fresh formulation of OTL-200 in the context of the IDS. (Orchard Data on file, 2019c) However, AEs related to surgical procedure were deemed unrelated to treatment with OTL-200 and have not been further characterised. Risks related to surgical procedures are well-characterized and known by health care professionals treating patients undergoing haematopoietic stem cell transplantation (HSCT).

Renal tubular acidosis

It has been suggested that patients with MLD may develop an underlying proximal (Type 2) renal tubular acidosis due to sulfatide accumulation in the renal tubules. These patients may be at risk of metabolic acidosis in various acute clinical conditions such as infection (Busulfex US PI, 2020).

Events of renal tubular acidosis and metabolic acidosis were defined based on venous blood gas parameters (blood pH and venous bicarbonate), urinary pH, and whether the acidotic event had occurred in combination with another clinical procedure (e.g. conditioning or general anaesthesia) or an acute clinical condition such an infection.

Renal tubular acidosis or metabolic acidosis was reported prior to treatment with OTL-200 in 16 subjects (55%) in the IDS. In total (including before and after treatment with OTL-200), 19 subjects (66%) have presented with events of renal tubular acidosis or metabolic acidosis.

Renal tubular acidosis was reported in eight subjects in the Pre-treatment phase, four subjects during the Treatment phase, and two subjects in the 3-month post-GT phase. The events occurring post-GT were considered to be related to the underlying disease and not OTL-200.

Metabolic acidosis was reported in three subjects in the Pre-treatment phase, four subjects during the Treatment phase, two subjects in the 3-month post-GT phase, one subject in the Short-term phase, and one subject in the Long-term phase. The events occurring post-GT were considered to be related to the underlying disease and acute clinical condition at the time of the event.

Two subjects who experienced AEs of renal tubular acidosis prior to the treatment subsequently experienced SAEs of metabolic acidosis. In one of these cases, the SAE of metabolic acidosis was temporally associated with concurrent febrile neutropenia and mucositis. In the other case, the event of metabolic acidosis was reported with a concurrent event of upper airways infection. Both events resolved following treatment of the event and concurrent medical condition and were considered related to the underlying disease.

There were no significant findings indicating that the treatment or concomitant medications employed in gene therapy play a critical role in the exacerbation of renal impairments.

Hepatobiliary disorders

Patients with MLD are known to be at increased risk of developing gallbladder abnormalities, including wall thickening and polyps, compared with patients with other lysosomal storage disorders or healthy patients. The deposition of accumulated sulfatide in visceral tissue has been implicated in these findings; the risk of gallbladder polyps evolving into carcinoma has been reported in MLD patients (Agarwal and Shipman, 2013, Kim et al., 2017).

Mild, non-serious gallbladder enlargement was reported in 22 subjects in the IDS during the Pre-treatment phase. None of the subjects treated with OTL-200 presented with hepatic impairment prior to treatment.

During the Follow-up phase, 16 subjects experienced hepatobiliary AEs that included newly reported events of gallbladder enlargement (three subjects); gallbladder polyps were reported in four subjects with pre-existing events of gallbladder enlargement. In two subjects, a cholecystectomy was performed due to findings of polyps >5 mm identified by ultrasound scan. Cholecystectomies were performed in consideration of the reported risk of

gallbladder polyps evolving into carcinoma. In both cases, the polyps were reported as SAEs.

After excluding event terms related to the gallbladder, 11 subjects (38%) in the IDS had events in the hepatobiliary disorders system organ class (SOC). These events included veno-occlusive liver disease, drug-induced liver injury, hepatomegaly, and hypertransaminasemia. Specifically, three patients in the CUP/HE programs experienced veno-occlusive liver disease. Two subjects experienced hypertransaminasemia (one Grade 1 and one Grade 2).

It is also important to highlight that hepatic veno-occlusive disease and hepatomegaly are known safety concerns related to busulfan conditioning (Ciurea and Andersson, 2009) and reported as ‘very common’ adverse reactions in Section 4.8 of the SmPC of the product which also reports that “Grade 3 elevated transaminases were reported in 24% of patients” (Busilvex SmPC, 2017).

SAEs

In the IDS, 20/29 subjects (69%) experienced SAEs during the post-treatment follow-up phase. SAEs were most frequently reported in the gastrointestinal disorders (31% of subjects), infections and infestations (28% of subjects), and nervous system disorders (21% of subjects) SOCs. In general, the SAEs observed were consistent with the known safety profile of busulfan (Busilvex SmPC, 2017) or symptoms of MLD. None of the SAEs were reported as related to OTL-200 by the investigator. (Orchard Data on file, 2019c)

Two subjects (7%) experienced SAEs of device-related infection in the Pre-treatment phase, and two subjects (7%) experienced SAEs of device-related infection in the Follow-up phase. Device-related infections are very common in patients with ports installed for central venous access. It is also important to note that central venous access was a requirement in all subjects to receive the conditioning regimen and to infuse OTL-200.

SAEs of metabolic acidosis were reported in two subjects, one of which was in the 3 Month post-GT phase and considered life-threatening and one of which was in the Short-Term Follow-up phase. MLD patients are at risk of metabolic

acidosis probably due to an underlying proximal (Type 2) renal tubular acidosis (Lorioli et al., 2015).

In addition, SAEs associated with MLD during the total Follow-up Post-treatment phase included dysphagia (n=4, 14%), motor dysfunction (n=4, 14%), gallbladder polyps (n=2, 7%), muscle spasticity (n=2, 7%), seizure (n=2, 7%), and foot deformity (n=1, 3%).

Patient MLDHE01 experienced SAEs of thrombocytopenia, anaemia, atypical haemolytic uremic syndrome (aHUS), and veno-occlusive disease (VOD) during the 3-month Post GT phase. A genetic analysis revealed that this patient (and his monozygous twin MLDHE02) was found to harbour a membrane cofactor protein (MCP) gene mutation, a defect shown to be associated with aHUS. Genetic analyses revealed a heterozygous deletion of complement factor H (CFH) R3 R1 and Ala353Val mutation of a complement gene encoding MCP, which has been associated with inadequate control of complement activation (Liszewski and Atkinson, 2015). The patient's clinical condition eventually improved, although his pre-collected unmanipulated autologous 'back-up' BM was re-infused on Day 66 to boost haematological recovery. The investigator considered all four of these SAEs to be unrelated to OTL-200. The busulfan conditioning regimen and patient age (<1 year) were reported as significant risk factors associated with VOD. Concurrent medication (busulfan), medical conditions (previous VOD and aHUS), and prolonged granulocyte colony stimulating factor (G-CSF) exposure were reported as other possible causes of the events of thrombocytopenia and anaemia. The busulfan conditioning regimen was reported as a possible cause of the event of aHUS.

Deaths

To date, three deaths have been reported in subjects treated with OTL-200 during the clinical development programme, all deemed to be unrelated to OTL-200. (Orchard Data on file, 2019c) Two of these deaths were attributed to rapid progression of underlying disease; in both cases the subjects would not be eligible for treatment in the post-market authorisation settings given the

approved indication. The third death was due to left hemisphere cerebral ischemic stroke, deemed unrelated to OTL-200 or MLD.

One of the subjects who died as a result of rapid progression was diagnosed with EJ MLD at 5 years of age and was treated after the onset of cognitive decline (i.e. IQ < 85). Post-treatment, motor and cognitive function continued to deteriorate. By 5 months post-treatment, the subject's motor function was limited with the ability to stand with support and crawl a few meters, with an estimated GMFC-MLD level 2 to 3. Difficulty in swallowing was first noted at 6 months post-treatment, and motor dysfunction was reported as serious by 9 months post-treatment. At approximately 14 months after treatment, the subject experienced worsening spasticity (NCI CTC Grade 4) and dysphagia (NCI CTC Grade 5). The parents declined placement of a PEG feeding tube, and the subject died approximately 15 months after receiving treatment. The investigator considered the death to be due to disease progression. (Orchard Data on file, 2019d)

The second subject who died as a result of disease progression was diagnosed with EJ MLD at 6 years of age and treated after a period of rapid disease progression between baseline and treatment. Post-treatment, progressive difficulties in walking and slightly slower speech were observed. At 5 months post-treatment, the subject experienced a continuous progression of disease, losing the ability to walk and speak followed by loss of hand, trunk, and head control. SAEs of spasticity and motor impairment were reported at approximately 5 months following treatment; events of motor impairment, spasticity, and dysphagia were reported as serious. The outcome of dysphagia was reported as fatal due to the inability to feed; the parents declined placement of a PEG feeding tube. Approximately 8 months after receiving treatment, the subject died. The investigator considered the events of motor dysfunction, muscle spasticity, and dysphagia as unrelated to OTL-200 and the death to be associated with the disease progression. (Orchard Data on file, 2019d)

Adverse drug reactions (ADRs)

Four subjects in the IDS (14%) experienced AEs considered by the investigator to be related to treatment with OTL-200. These events were reported as antibody test positive (n=4, 14%). All were Grade 2, and none were serious. One patient also had a Grade 2 AE of positive anti-platelet antibodies that was reported as related to treatment; however, this entry was subsequently determined to be an error in the electronic case report form (eCRF), as verified by the investigator, who did not consider the AE of positive anti-platelet antibodies to be related to OTL-200 treatment. (Orchard Data on file, 2019c)

ADRs potentially attributable to myeloablative conditioning (busulfan)

The review process for the selection of adverse drug reactions (ADRs) potentially related to myeloablative conditioning was conducted using the Integrated Data Set and was developed to ensure consideration of many aspects of the data. (Orchard Data on file, 2019c) The specific process included several steps. Firstly, the preferred terms were further reviewed and compared with the SmPC of busulfan and other gene therapies (Zynteglo® and Strimvelis®) where similar myeloablative conditioning regimens have been used. AEs were flagged at the preferred term level, and then an iterative process involving the principles above was applied to the preferred terms in each system organ class (SOC).

Secondly, for the flagged preferred terms, further review of subject-level data was performed, including an assessment of relevant medical history, co-morbidities, and other AEs.

Finally, there was a clinical evaluation, which included, as appropriate, consideration of similar PTs, biological plausibility, nature and timing of the events, the underlying disease, and incidence of the event in the paediatric population. After a comprehensive final assessment, 32 PTs from 14 SOCs were determined by the Sponsor to be potentially attributable to myeloablative conditioning. Of these 32 PTs, the ones reported as ‘very common’ in Section 4.8 of the busulfan SmPC (Busilvex SmPC, 2017) are shown in Table C11.

Table C23: Adverse events potentially related to myeloablative conditioning

System organ class	Very common ≥10%
Blood and lymphatic system disorders	Febrile neutropenia, neutropenia
Gastrointestinal disorders	Stomatitis, vomiting
General disorders and administration site conditions	Mucosal inflammation
Hepatobiliary disorders	Hepatomegaly, veno-occlusive liver disease
Metabolism and nutrition disorders	Metabolic acidosis

Immune response

AAAs were transiently detected in four of 29 subjects treated with the fresh formulation of OTL-200 without any obvious clinical impact. For Study 201222 (where AAA were tested from 3 months post-treatment onwards), no subjects have tested positive for AAA and none of the treated subjects under EAPs tested positive for antibodies at the baseline visit. (Orchard Data on file, 2019c)

Antibody titres in all four subjects were generally low and at the time of the data cut, all had resolved to negative test results, either spontaneously (n=1) or after one cycle of rituximab (n=3).

In all four subjects with positive AAA tests, there was no evidence of a negative clinical effect observed in the post-treatment ARSA activity of PB/BM (or any other relevant cellular subpopulations) nor in the ARSA activity within CSF. It is important to highlight that the transient detection of AAA did not have any obvious impact on the clinical benefits of OTL-200 or on its safety profile in these subjects. Furthermore, and from a mechanistic perspective, AAA are not anticipated to interfere with the functionality of ARSA activity in brain due to the limitations of antibodies to cross the blood-brain barrier. All subjects that had positive AAA tests were alive at the time of the data cut for the preparation of this dossier and continue to be followed.

Replication competent lentivirus (RCL)

Molecular monitoring of RCL has been carried out in the clinical development programme, using the following preliminary screening tests: a) enzyme-linked immunosorbent assay (ELISA) for HIV p24 antigen; b) DNA polymerase chain reaction (PCR) for vesicular stomatitis virus (VSV-G env); and c) reverse transcriptase PCR for HIV-pol ribonucleic acid (RNA). (Orchard Data on file, 2019c)

Anti-HIV p24 antibodies were also searched. The tests were performed at baseline and after 1, 3, 6, 12, and 24 months. If one of the preliminary tests resulted in a positive assessment, the tests were repeated at the next planned follow-up visit. If two of three of the preliminary screening tests were positive, a confirmatory culture test would have been performed.

At the time of writing this dossier, there were no confirmed reports of positive results for RCL. More specifically, in the Integrated data set, six subjects (21%) tested positive for vesicular stomatitis virus glycoprotein G envelope (VSV-G env) at Baseline, before exposure to OTL-200. During the course of post-GT follow-up, positive findings for VSV-G env were also reported for several subjects. However, other RCL screening tests remained negative for these subjects and the analysis of later time points for VSV-G env were negative for all except one patient. The positive results at Baseline before exposure to OTL-200, therefore, suggest false positive results possibly due to contamination with a source of VSV-G DNA either (i) at the time of PBMC preparation at the clinical site or (ii) during the DNA extraction and assay process.

Abnormal clonal proliferation/insertional mutagenesis

Evidence of abnormal haematopoietic clonal proliferation was assessed by clinical and laboratory surveillance and BM examination. (Orchard Data on file, 2019c) As reported in more detail in the clinical study report (CSR) modular appendices, there was no evidence of clonal expansion as assessed by BM and PB lymphocytes karyotype, morphological analyses, immune phenotyping, and T-cell receptor repertoire.

In addition, integration site analysis of DNA from blood and BM samples from treated subjects was conducted to monitor the nature and distribution of vector integration sites. The clonal composition of the transduced cell graft was analysed for identification of potential clonal expansion.
The integration site analysis performed on patients' bone marrow and peripheral blood-derived cells on all 29 treated MLD patients showed overall a polyclonal pattern of haematopoietic reconstitution, without dominant clones persisting over time or other signs of genotoxicity. Occasional clones with relative abundances above 20% were sporadically detected, due to the very early time phases of haematopoietic reconstitution and/or due to the low amount DNA available for integration site analysis, thus likely representing a method artefact.

To date, no cases of malignant clonal expansion, malignancy or AEs indicative of oncogenic transformation have been reported in the clinical development programme of OTL-200, and there has been no evidence of aberrant clonal behaviour based on insertion site analysis.

The data above are therefore in agreement with the results reported from previous studies which revealed a highly polyclonal reconstitution of hemopoiesis in all analysed patients without evidence of expanding or dominant clones (Sessa et al., 2016a, Biffi et al., 2013).

9.7.2.2 Study 205756 (cryopreserved formulation)

Table C24: Summary of AEs by treatment phase (number of subjects and occurrences)

System organ class / Preferred Term	Pre-Treatment (n=6)	Treatment (n=6)	Acute (n=5)	3 months post-treatment (N=5)	Short-term (n=4)	Follow-up (n=5)
Any AE	6 (100%) 28	3 (50%) 6	1 (20%) 1	5 (100%) 42	4 (100%) 18	5 (100%) 61
Blood and lymphatic system disorders	2 (33%) 3	1 (17%) 1	0	5 (100%) 10	0	5 (100%) 10
Anaemia	2 (33%) 2	0	0	0	0	0
Febrile neutropenia	0	0	0	5 (100%) 6	0	5 (100%) 6
Neutropenia	1 (17%) 1	1 (17%) 1	0	3 (60%) 4	0	3 (60%) 4
Gastrointestinal disorders	2 (33%) 2	0	0	4 (80%) 6	0	4 (80%) 6
Constipation	1 (17%) 1	0	0	1 (20%) 1	0	1 (20%) 1
Diarrhoea	1 (17%) 1	0	0	1 (20%) 1	0	1 (20%) 1
Stomatitis	0	0	0	4 (80%) 4	0	4 (80%) 4
General disorders and administration site conditions	2 (33%) 3	0	0	2 (40%) 2	2 (50%) 3	2 (40%) 5
Gait disturbance	0	0	0	0	1 (25%) 1	1 (20%) 1
Pyrexia	2 (33%) 3	0	0	2 (40%) 2	2 (50%) 2	2 (40%) 4
Hepatobiliary disorders	3 (50%) 3	1 (17%) 1	0	3 (60%)	0	3 (60%) 3
Cholecystitis acute	0	0	0	1 (20%) 1	0	1 (20%) 1
Gallbladder enlargement	3 (50%) 3	0	0	1 (20%) 1	0	1 (20%) 1
Hepatomegaly	0	0	0	1 (20%) 1	0	1 (20%) 1
Hypertrans-aminasaemia	0	1 (17%)	0	0	0	0

System organ class / Preferred Term	Pre-Treatment (n=6)	Treatment (n=6)	Acute (n=5)	3 months post-treatment (N=5)	Short-term (n=4)	Follow-up (n=5)
Infections and infestations	4 (67%) 7	3 (50%) 3	0	2 (40%) 3	3 (75%) 10	3 (60%) 13
Adenovirus infection	1 (17%) 1	0	0	0	0	0
Bacterial disease carrier	0	1 (17%) 1	0	0	0	0
Cytomegalovirus infection	0	1 (17%) 1	0	0	0	0
Device related infection	2 (33%) 2	1 (17%) 1	0	0	0	0
Ear infection	1 (17%) 1	0	0	0	0	0
Enterovirus infection	0	0	0	1 (20%) 1	0	1 (20%) 1
Gastroenteritis	0	0	0	0	1 (25%) 1	1 (20%) 1
Haemophilus infection	1 (17%) 1	0	0	0	0	0
Helicobacter infection	1 (17%) 1	0	0	0	0	0
Herpes zoster	0	0	0	0	1 (25%) 1	1 (20%) 1
Klebsiella infection	0	0	0	1 (20%) 1	0	1 (20%) 1
Nasopharyngitis	0	0	0	0	1 (25%) 1	1 (20%) 1
Otitis media	0	0	0	0	1 (25%) 1	1 (20%) 1
Otitis media acute	0	0	0	0	1 (25%) 1	1 (20%) 1
Pharyngitis	0	0	0	0	2 (50%) 2	2 (40%) 2
Sepsis	0	0	0	1 (20%) 1	0	1 (20%) 1
Upper respiratory tract infection	1 (17%) 1	0	0	0	3 (75%) 3	3 (60%) 3
Injury, poisoning and procedural complications	0	0	0	1 (20%) 2	0	1 (20%) 2
Arthropod bite	0	0	0	1 (20%) 1	0	1 (20%) 1
Transfusion reaction	0	0	0	1 (20%) 1	0	1 (20%) 1

System organ class / Preferred Term	Pre-Treatment (n=6)	Treatment (n=6)	Acute (n=5)	3 months post-treatment (N=5)	Short-term (n=4)	Follow-up (n=5)
Investigations	3 (50%) 5	1 (17%) 1	0	3 (60%) 4	3 (75%) 4	5 (100%) 8
Antithrombin III decreased	0	0	0	1 (20%) 1	0	1 (20%) 1
Blood immunoglobulin E increased	2 (33%) 2	0	0	0	2 (50%) 2	2 (40%) 2
Cytomegalovirus test positive	0	0	0	1 (20%) 1	0	1 (20%) 1
Fibrin D dimer increased	0	0	0	1 (20%) 1	0	1 (20%) 1
Giardia test positive	0	1 (17%) 1	0	0	0	0
Herpes simplex test positive	1 (17%) 1	0	0	0	0	0
Moraxella test positive	0	0	0	0	1 (25%) 1	1 (20%) 1
Oxygen saturation decreased	1 (17%) 1	0	0	0	0	0
Roseolovirus test positive	0	0	0	1 (20%) 1	0	1 (20%) 1
Staphylococcus test positive	1 (17%) 1	0	0	0	0	0
Streptococcus test positive	0	0	0	0	1 (25%) 1	1 (20%) 1
Metabolism and nutrition disorders	2 (33%) 2	0	0	1 (20%) 1	0	1 (20%) 1
Failure to thrive	1 (17%) 1	0	0	0	0	0
Fluid retention	0	0	0	1 (20%) 1	0	1 (20%) 1
Metabolic acidosis	1 (17%) 1	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	2 (40%) 2	0	2 (40%) 2
Anthralgia	0	0	0	1 (20%) 1	0	1 (20%) 1
Back pain	0	0	0	1 (20%) 1	0	1 (20%) 1

System organ class / Preferred Term	Pre-Treatment (n=6)	Treatment (n=6)	Acute (n=5)	3 months post-treatment (N=5)	Short-term (n=4)	Follow-up (n=5)
Renal and urinary disorders	0	0	0	1 (20%) 1	0	1 (20%) 1
Renal tubular acidosis	0	0	0	1 (20%) 1	0	1 (20%) 1
Respiratory, thoracic and mediastinal disorders	1 (17%) 1	0	0	1 (20%) 2	0	1 (20%) 2
Respiratory distress	1 (17%) 1	0	0	1 (20%) 1	0	1 (20%) 1
Rhinorrhea	0	0	0	1 (20%) 1	0	1 (20%) 1
Skin and subcutaneous tissue disorders	2 (33%) 2	0	1 (20%) 1	3 (60%) 6	1 (25%) 1	5 (100%) 8
Blister	0	0	0	1 (20%) 1	0	1 (20%) 1
Drug eruption	1 (17%) 1	0	0	0	0	0
Hyperkeratosis	0	0	0	1 (20%) 1	0	1 (20%) 1
Rash	0	0	0	1 (20%) 1	0	1 (20%) 1
Rash erythematous	0	0	0	1 (20%) 2	0	1 (20%) 2
Rash generalised	0	0	1 (20%) 1	0	0	1 (20%) 1
Rash maculo-papular	1 (17%) 1	0	0	1 (20%) 1	0	1 (20%) 1
Urticaria	0	0	0	0	1 (25%) 1	1 (20%) 1

Source: Orchard Therapeutics Data on file.

OTL-200 was well-tolerated in all subjects with no treatment-related adverse events. (Orchard Data on file) Overall, the safety profile observed in this study until the cut-off is consistent with previous experience. Although the investigators could only assess an event as related or unrelated to OTL-200 (due to limitation of electronic case report form [eCRF] design), the nature, time to onset, and frequency of the AEs reported in this study are expected for patients who undergo conditioning or are suffering from MLD. The frequency and severity of events observed is not unexpected.

None of the subjects had positive RCL screening tests at the time of reporting.

At the time of reporting, no cases of malignancy or AEs indicative of oncogenic transformation had been reported. There was no evidence of abnormal clonal proliferation as assessed by clinical and laboratory surveillance and BM examination.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

As previously discussed, the safety data presented are from the full IDS, and not from the indicated population subset. However, as the majority of the IDS fall within the indicated population there is no reason to suggest that there will be a difference in safety profiles between the IDS and the indicated population.

Treatment with the fresh formulation of OTL-200 has been shown to be especially well-tolerated in pre-symptomatic patients included in the integrated analysis (n=20/29). (Orchard Data on file, 2019c) Numerically, patients who were pre-symptomatic at the time of treatment experienced fewer AEs during all study phases compared with those who were symptomatic (Table C26). The biggest numerical difference was during the Treatment phase, where 45% of pre-symptomatic patients group experienced at least one AE compared with 89% in the symptomatic group. None of the events in the Treatment phase in either group were considered as related to OTL-200; therefore, the difference in AEs in the Treatment phase between groups is likely indicative of the overall underlying disease status of the symptomatic patients. Events in the Treatment phase in pre-symptomatic subjects included metabolic acidosis (two subjects, 10%) and renal tubular acidosis, hepatomegaly, respiratory tract infection, klebsiella test positive, staphylococcus test positive, rash erythematous, eczema, head injury, procedural pain and bone pain (each in one subject, 5%). Events in the Treatment phase in symptomatic subjects included renal tubular acidosis (three subjects, 33%), metabolic acidosis (two subjects, 22%), increased

levels of ALT and AST, nausea, hepatomegaly, skin infection, and bradyarrhythmia (each in one subject, 11%).

Table C25: Adverse events by symptomatic status at the time of treatment (Integrated data set)

	Pre-symptomatic (n=20)			Symptomatic (n=9)		
Category	**n**	**%**	**M**	**n**	**%**	**M**
Pre-treatment						
AEs	20	100	55	9	100	24
SAEs	2	10	2	0	0	0
Treatment phase*						
AEs	9	45	12	8	89	11
AE by grade						
Grade 1	6	30	6	4	44	4
Grade 2	2	10	2	1	11	1
Grade 3	4	20	4	4	44	6
Grade 4–5	0	0	0	0	0	0
Follow-up post-treatment phase						
AEs	20	100	321	9	100	144
Treatment-related AEs	4	20	6	0	0	0
AEs leading to withdrawal	1	5	1	2	22	2
SAEs	14	70	25	6	67	17
Deaths	1	5	1	2	22	2
Treatment-related SAEs	0	0	0	0	0	0
AEs by grade						
Grade 1	19	95	83	9	100	34
Grade 2	19	95	138	8	89	36
Grade 3	20	100	96	9	100	68
Grade 4	2	10	3	4	44	4
Grade 5	1	5	1	2	22	2

* No treatment-related AEs, AEs leading to withdrawal, SAEs or deaths occurred during the treatment phase in either subgroup population.
AE, adverse event; M, number of events; SAE, serious adverse event.

In terms of the most commonly reported AEs by SOC, both groups were comparable and experienced similar types of events; however, the order was altered. In the pre-symptomatic group, the most commonly occurring SOCs were infections and infestations (95%), investigations (90%), blood and lymphatic system disorders (75%), gastrointestinal disorders (75%) and general disorders and administrative site conditions (70%). In the symptomatic group, the most commonly occurring SOCs were blood and lymphatic system

disorders (89%), gastrointestinal disorders (89%), general disorders and administrative site conditions (89%), nervous system disorders (89%) and infections and infestations (78%).

Only 35% of the pre-symptomatic subjects experienced nervous system-related AEs during the Follow-up post-GT phase compared with 89% in the symptomatic group, which is expected given the involvement of the nervous system in patients with MLD. Events associated with MLD were more common in subjects who were symptomatic at the time of treatment than in subjects who were pre-symptomatic (Table C27).

Table C26: Adverse events related to MLD by symptomatic status at the time of treatment

Preferred term, n (%)	Pre-symptomatic (n=20)				Symptomatic (n=9)			
	3-month post-treatment (n=20)	Short term (n=20)	Long term (n=9)	Total follow-up post-treatment (n=20)	3-month post-treatment (n=9)	Short term (n=9)	Long term (n=7)	Total follow-up post-treatment (n=9)
Gait disturbance	2 (10)	6 (30)	0	8 (40)	3 (33)	3 (33)	1 (14)	7 (78)
Motor dysfunction	1 (5)	2 (10)	0	3 (15)	1 (11)	5 (56)	0	6 (67)
Muscle spasticity	0	1 (5)	1 (11)	2 (10)	1 (11)	5 (56)	1 (14)	7 (78)
Aphasia	0	0	1 (11)	1 (5)	1 (11)	4 (44)	0	5 (56)
Ataxia	0	0	0	0	2 (22)	3 (33)	0	5 (56)
Dysarthria	0	1 (5)	0	1 (5)	1 (11)	3 (33)	0	4 (44)
Cognitive disorder	0	0	1 (11)	1 (5)	0	3 (33)	0	3 (33)
Dysphagia	0	0	1 (11)	1 (5)	0	3 (33)	0	3 (33)
Renal tubular acidosis	0	0	0	0	2 (22)	0	0	2 (22)
Metabolic acidosis	1 (5)	1 (5)	0	2 (10)	1 (11)	0	1 (14)	2 (22)
Gallbladder enlargement	0	0	1 (11)	1 (5)	1 (11)	1 (11)	0	2 (22)
Gallbladder polyp	0	3 (15)	0	3 (15)	0	1 (11)	0	1 (11)
Seizure	0	1 (5)	0	1 (5)	0	0	1 (14)	1 (11)
Foot deformity	0	0	0	0	0	1 (11)	0	1 (11)

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

As already described in Section 9.4.2, the efficacy results presented in this submission is from a post-hoc analysis of data from the patients who fall within the approved indication: [redacted] patients with pre-symptomatic Late Infantile (PS LI) MLD, [redacted] with pre-symptomatic Early Juvenile (PS EJ) and [redacted] with early-symptomatic Early Juvenile (ES EJ) MLD (i.e. [redacted] out of 29 patients treated with OTL-200 fresh formulation).

Beyond that, no other evidence synthesis or meta-analysis has been undertaken, other than a focus on the relevant populations for analysis as below.

As both the registrational study and EAPs are open-label, non-comparative studies, the longitudinal natural history OSR-TIGET study, was considered the most relevant source of comparative data, especially as it was done in the same allowing a comparison between clinical management including OTL-200 vs. usual clinical management without OTL-200. Data from subjects that were age and disease subtype matched from the NHx study was used at the primary comparative cohort group in order to ensure a representative and relevant natural history cohort/control for comparison. Analysis using data from untreated affected siblings in the NHx study were also undertaken.

Among the 31 subjects included as a non-concurrent comparator group from the OSR-TIGET NHx study, 19 subjects met the protocol-defined classification for LI MLD and 12 subjects met the protocol-defined classification for EJ MLD.

The limited natural history data in pre-symptomatic or very early symptomatic subjects is justified due to the time from first noticeable symptoms to study enrolment and due to propositions to participate in non-interventional studies being unethical when investigational therapies are available.

In order to minimise the bias linked to differences in age and disease-severity at study entry, in addition to prospective data collection following enrolment in the NHx study, retrospective data available prior to enrolment was also collected with the objective of reconstructing the disease progression of these subjects as much as possible. This approach was applied to the clinical outcomes more amenable to retrospective reconstruction (i.e. gross motor function dynamics using time to acquisition of motor milestones from birth to 18 months of age and Gross Motor Function Classification MLD (GMFC-MLD) from 18 months of age onwards). This strategy enabled a more comprehensive age-matching analysis between the treated and the natural history comparator cohorts.

At the time of the MAA, only data from six patients treated in Study 205756 was available. Due to the recent initiation of this study and short follow-up available, data from this study were not included in the integrated analysis.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The safety and efficacy of OTL-200 has been demonstrated in a comprehensive clinical programme involving 35 patients treated in two clinical studies (the registrational study 201222 and the clinical study 205756) and three Expanded Access Programs (EAPs). Twenty nine of the 35 patients in the clinical programme were treated with the fresh formulation of OTL-200 (OTL-200-f) and six patients treated with the cryopreserved formulation (OTL-200-c).

The fresh formulation data include 20 patients treated in registrational study 201222 (Clinicaltrials.gov NCT01560182) and nine patients treated in three expanded access programmes (EAPs). Registrational Study 201222 and the EAPs have a similar study design and were conducted by the same team at the same centre, and these patients have been combined to make an integrated data set (IDS; n=29). (Orchard Data on file, 2019b)

Efficacy results from patients treated with OTL-200-f demonstrated that the patients who benefitted from treatment were (i) Late Infantile and Early Juvenile patients treated pre-symptomatically (PS LI and PS EJ) (i.e. before clinical manifestations of the disease; and (ii) Early Juvenile patients with early clinical manifestations of the disease (ES EJ). (i.e. still had the ability to walk independently and cognitive decline had not started). As such, the CHMP approved indication for OTL-200 is restricted to these patients.

Hence, this submission presents efficacy data from a post-hoc analysis focussed on the patients within the IDS who fall within the indication. In total [redacted] out of 29 patients in the IDS were included in this analysis: [redacted] patients with pre-symptomatic Late Infantile (PS LI) MLD, [redacted] patients with pre-symptomatic Early Juvenile (PS EJ) MLD and [redacted] patients with early-

symptomatic Early Juvenile (ES EJ) MLD (referred to as the indicated population).

[redacted] patients in the IDS have been excluded from the *post hoc* efficacy analysis as they would not meet the criteria for treatment using the refined inclusion criteria for the indication. Suggest adding topline the reasons why the [redacted] are excluded to drive home the indicated population criteria i.e. excluded due to IQ < 85 or disease/symptom progression prior to therapy.

When OTL-200 is administered before the rapidly progressive phase of the disease, treatment effects observed in gross motor function, cognition, brain imaging and peripheral nervous system in PS LI, PS EJ and ES EJ MLD subjects show that OTL-200 provides meaningful clinical benefits in the treatment of PS LI, PS EJ and ES EJ variants of the disease by preserving cognitive function, delaying time to severe motor disability and slowing down brain demyelination and atrophy. (Orchard Data on file, 2019b)

Durable and stable peripheral engraftment of gene-corrected cells was observed from 1 month post OTL-200 administration in all evaluable subjects, as indicated by %LV+ values well above the protocol-defined target of 4% and persistent VCN in CD34+ cells isolated from the BM and mPB throughout the follow-up period. These biological findings demonstrated a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting microglial reconstitution and the long-term production of ARSA. (Orchard Data on file, 2019b)

Reconstitution of ARSA activity in the haematopoietic system was observed in all MLD subjects in the IP (n=25), with a progressive reconstitution of ARSA levels in PBMCs that reached values within the normal reference range by 3 months post-treatment and remained stable within or above the normal range throughout the duration of the follow-up. (Orchard Data on file, 2019b) These results provide indirect evidence that genetically modified cells, particularly of the myeloid lineage, effectively migrated to the CNS, engrafted, and produced ARSA enzyme activity within or above the normal range. Engraftment and ARSA levels in the patients treated with the cryopreserved

formulation (OTL-200-c) are comparable those seen in the IP at the same time points. (Orchard Data on file)

PS LI, PS EJ and ES EJ MLD subjects treated before the onset of overt symptoms showed normal motor development, stabilisation, or delay in the rate of progression of motor dysfunction as measured by GMFM total score (%). The mean difference between treated PS LI subjects and age matched untreated NHx LI subjects was 71.0% at Year 2 and 79.8% at Year 3. Similarly, the mean difference between treated PS EJ subjects and age-matched untreated NHx EJ subjects was 52.4% at Year 2 and 74.9% at Year 3. These treatment differences were statistically significant in favour of OTL-200. [redacted] (Orchard Data on file, 2019b)

[redacted] (Orchard Data on file, 2019b)

[redacted] (Orchard Data on file, 2019b)

[redacted]

[redacted]

[redacted]

[redacted]

These results suggest that treatment with OTL-200 prevents, stabilises, or markedly delays the progressive demyelination and atrophy typically observed as a hallmark of MLD.

Quality-adjusted survival analyses were conducted to explore the difference in the composite endpoints of time to severe motor impairment or death (sMFS) and time to severe cognitive and motor impairment-free survival (sCMFS) in treated subjects compared with the NHx population, thereby reflecting the quality of life of subjects and families/caregivers.

The sMFS analysis showed that, , [redacted] (Orchard Data on file, 2019b)

[redacted]

[redacted]

[redacted]

[redacted] (Orchard Data on file, 2019b)

[redacted]

In order to uncover the degree of cognitive impairment extending beneath the floor effect of 40 in treated and NHx subjects, developmental quotient (DQ) and age-equivalent scores were used as exploratory analysis of cognitive function. (Orchard Data on file, 2019b)

[redacted]

[redacted]

Age-equivalent scores showed normal acquisition of cognitive skills in the majority of treated LI and EJ subjects at chronological ages at which untreated NHx subjects showed severe cognitive impairment.

These results support the positive treatment effects of OTL-200 on cognition and provide further evidence of the benefit of OTL-200 to treat the key clinical manifestations of the disease when administered before the onset of the rapidly progressive decline.

OTL-200 was well-tolerated with no treatment-related serious adverse events and no evidence of abnormal clonal proliferation (ACP). (Orchard Data on file, 2019c)

The Number Needed to Treat (NNT) and Number Needed to Harm (NNH) have not been calculated.

The cryopreserved formulation of OTL-200 will be the one that is commercially available. Preliminary clinical data from Study 205756 support the *in vitro* analytical comparability and *in vivo* comparability data between the fresh and cryopreserved formulations of OTL-200.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths

The short- and long-term efficacy and safety outcomes assessed in all studies presented here were clinically relevant and objective.

The studies were conducted by a European centre (Ospedale San Raffaele - Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy), and the patients recruited are representative of early-onset MLD patients seen in clinical practice in the UK.

The clinical evidence presented here is from a clearly-identified and clinically-identifiable population that will benefit from treatment with OTL-200.

Although the studies had no comparator for ethical and practical reasons, the studies used a population selected from a natural history (NHx) study run by the same centre (OSR-TIGET) for comparative purposes. Data collected as part of this study are directly comparable to the study endpoints used in the OTL-200 studies presented here, and the same definitions of LI and EJ MLD were used to classify subjects. In addition, [redacted] of the [redacted] subjects in the IP have or had siblings enrolled in the NHx study, and these matched siblings are particularly appropriate comparators as untreated siblings with the same genotype and family environment are predicted to show very similar disease progression over time (Mahmood et al., 2010).

Limitations

The studies presented here are non-randomised, with no comparator arm, and include only a small number of patients. The lack of a comparator arm is as a result of ethical and practical considerations. However, early-onset MLD is an ultra-rare, life-limiting condition for which there is currently no curative treatment approved for use. Consequently, these limitations in study design and methodology, coupled with the small number of patients, are inevitable features of undertaking a clinical trial for an active treatment for patients with such a rare disease.

The clinical evidence presented here consists of interim results from surviving patients with only 3 years (Study 201222 and the EAPs) or less (Study 205756) of follow-up data. However, follow-up is continuing, and data are already available for two LI patients with more than 7 years of follow up, one of the longest periods of data collection available for a gene therapy.

The clinical evidence presented here is drawn largely from a patient population treated with the fresh formulation of OTL-200, and not the cryopreserved formulation that will be commercially available. However, preliminary results from an ongoing study (Study 205756) indicate that the efficacy and safety of the cryopreserved formulation matches that of the fresh formulation and offers patients the same level of therapeutic effects.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The clinical evidence base for OTL-200 is relevant to the scope specified in Table A1 for the following reasons:

Population

The clinical studies include patients with LI and EJ MLD and are directly relevant to the patient population seen in UK clinical practice. In addition, the studies were conducted by a European centre (Ospedale San Raffaele - Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy).

Comparator

The comparator, best supportive care (BSC), reflects current clinical practice in the UK. It aims to manage disease complications and support quality of life as far as possible but does not target the root cause of the progressive motor and cognitive decline or halt progression of the disease.

In a recent MLD UK Health Model Advisory Board, the UK experts expressed the view that allogeneic HSCT would not be used routinely to treat the OTL-200-indicated population of MLD patients even in a world without gene therapy, therefore making it an inappropriate comparator for OTL-200, which is further supported by several recent publications.

Van Rappard et al. in their review of therapeutic options in MLD (van Rappard et al., 2015) found that HSCT does not seem to be beneficial for overtly-symptomatic patients or patients with the aggressive LI onset type. Inconsistent results have been reported for asymptomatic patients.

Similar results were seen by Beschle and colleagues (Beschle et al., 2020), who noted that it takes up to 12–24 months until allogeneic HSCT treatment effect becomes apparent because of the slow replacement of resident tissue, which in turn makes HSCT ineffective in children with the rapidly progressive Late Infantile form and in juvenile patients with symptoms. Deterioration in cognitive function in this cohort paralleled deterioration in gross motor function. Some patients exhibited rapid and severe disease progression after allogeneic HSCT and deteriorated more rapidly than non-transplanted patients, indicating a triggering effect of HSCT on disease progression.

Tan et al. on behalf of the Inborn Errors Working Party of EBMT (Tan et al., 2019) noted that there is no role for HSCT in Sanfilippo syndrome (MPS III) or infantile Metachromatic Leukodystrophy (MLD). In MLD, transplant failure may be largely attributable to the slow and gradual replacement of resident tissue macrophages and microglia populations by donor-derived progeny compared with the rapid progression of disease. Furthermore, donor-derived microglial cells may secrete insufficient amounts of enzyme to correct neuronal tissue in these LSDs. Ex-vivo stem cell gene therapy of autologous HSC improves graft enzyme delivery and has been shown to be dramatically beneficial in modifying disease progression in infantile MLD. (Tan et al., 2019, Biffi et al., 2013)

Outcomes

The outcomes listed in the NICE scope were captured in the clinical and HRQoL studies.

Efficacy

The clinical studies demonstrate strong evidence for the efficacy of OTL-200 in treated patients. Effective treatment of MLD would lead to significant benefit across a variety of stakeholder groups, including patients, caregivers, healthcare providers and society at large.

Most children treated with OTL-200 have shown:

- normal development of motor function; and

- maintenance of cognitive skills throughout the follow-up period to date.

As a result, treatment with OTL-200:

- maintained daily activities of living, such as walking and self-feeding, and allowed children to attend school and build normal relationships with family members and carers; and, importantly, their peers.
- sustained the time during which the children are comfortable and alert.

In addition to providing direct clinical benefits to the patient, OTL-200 is anticipated to benefit families and carers by improving wellbeing and reducing time spent caring, leading to productivity gains. A reduction in the length and intensity of caring may also reduce the risk of mental health problems and family difficulties.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The company is not aware of any factors that might influence the external validity of study results to patients in routine clinical practice.

Limitations in study design and methodology (open-label, no comparator arm) coupled with the small number of patients are inevitable features of undertaking a clinical trial in patients treated with a gene therapy. However, due to the ultra-rare status of the disease, the studies and EAPs are likely to have enrolled a substantial proportion of the relevant patient population. This means that the studies reflect the range of patients encountered in clinical practice, and therefore the external validity of the study results presented is likely to be high.

The cryopreserved formulation of OTL-200 will be the one that is commercially available. Although the majority of the results presented here are for the fresh formulation, preliminary clinical data from Study 205756 support the *in vitro* analytical comparability and *in vivo* comparability data between the fresh and cryopreserved formulations of OTL-200. This high comparability between the fresh and cryopreserved formulations provides ourselves and EMA confidence

that the cryopreserved product will also provide comparable clinical benefits for MLD patients.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable.

10 Measurement and valuation of health effects

10.1 Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

MLD is a devastating life-threatening disease with a severe prognosis and extremely poor quality of life for all affected patients, especially in young children with the more aggressive forms of the disease.

MLD has physical, gross motor function, and cognitive/behavioural impacts on patients. (Eichler et al., 2016) Patients experience cognitive decline, loss of speech, swallowing difficulties, pain, constipation, stiffness, and vision/respiratory problems. They experience limited relationships with peers and siblings, problems with social interaction and emotional discomfort. They may feel pain even when unable to communicate, and the sensation may be a consequence of spasticity, constipation, or peripheral neuropathy, and may affect sleep. The deterioration of gross motor function, that is, loss of motor skills, walking difficulties, inability to sit or stand without support, and imbalance, occurs rapidly as the disease progresses, resulting in a loss of autonomy. The disease progresses to end-of-life in a decerebrated state and premature death. (Biffi et al., 2008, Elgun et al., 2019, van Rappard et al., 2015)

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

There are no studies that describe HRQL over the disease course of MLD. However as described in section 6.1. and 7.1. MLD is a progressive disease with rapid deterioration of motor or cognitive functions which culminates in a decerebrated state and early death. Therefore, the patient's health-related quality of life (HRQL) is likely to deteriorate as the disease progresses. A recently completed utility study commissioned by Orchard Therapeutics has shown that utility values for Late Infantile and juvenile MLD patients decreased with progressive decline in motor function (as measured by GMFC-MLD) and cognitive function (measured by DQ). A detailed description of the utility study and the results are provided in section 10.4.

10.2 HRQL data derived from clinical trials

10.2.1 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case.

There were no HRQL data collected in the clinical trials.

10.3 Mapping

10.3.1 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Not applicable.

10.4 HRQL studies

10.4.1 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

HQRL studies were searched for as part of the systematic literature review described in Section 9.1 (see also Appendix B).

10.4.2 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

The literature search identified no studies that assessed HRQL in MLD patients. However since completion of the SLR, a utility study commissioned by Orchard Therapeutics has been completed. Details of the study are provided in Table C28 and described below. The aim of this study was to elicit utility values for Late Infantile and juvenile MLD in the UK. Health states were developed through a literature review and qualitative interviews with clinicians (N=[redacted]) and caregivers (N=[redacted]). Health states were defined by the Gross Motor Function Classification (GMFC-MLD1 to 6) and by Development Quotient (DQ) scores for three cognitive functioning levels: normal functioning / mild impairment (DQ> 70); moderate impairment (DQ > 55 to ≤ 70); and severe impairment (DQ < 55) for juveniles (30 months to 16 years of age). Late Infantile (under 30 months) health states were defined by GMFC- MLD only. Problems such as swallowing, muscle contractions, digestive issues, seizures, and sleep problems were amongst the various symptoms that were reported. Clinicians reported that patients experienced significant symptoms from GMFC-MLD2 onwards, with degree of severity increasing from stages 2-6. Health states were valued by members of the UK general public (n=[redacted]) who completed a visual analogue scale (VAS) and time trade-off (TTO) assessment, including lead-time method. Amongst Late Infantile states, the mean TTO values ranged from [redacted] (GMFC-MLD1) to [redacted] (GMFC-MLD6). Juvenile states had considerably lower utility values than infantile states and worsened with cognitive status. In the normal cognitive group, the mean utility values ranged from [redacted] (GMFC-MLD1) to [redacted] (GMFC-MLD4). In the moderate group, the mean scores ranged from [redacted] (GMFC-MLD0) to [redacted] (GMFC-MLD6) and from [redacted] (GMFC-MLD0) to [redacted] (GMFC-MLD6) in the severe group.

Table C27: Study characteristics and data extracted from included health state utility studies

Study	Description of population and recruitment method	Country	Sample size and response rate	Intervention and comparator	Description of health states and adverse events	Methods of elicitation and valuation	Results	Appropriateness of study for cost-effectiveness evaluation
Nafees et al 2020	Members of the general public (18 years and over), able to communicate written and orally in English and understand the study were recruited across the UK from newspaper advertisements and existing database of volunteers.	UK	UK The first round involved [redacted] members of the general public While the second round involved [redacted] members of the general public. Response rate was not reported.	N/A	GMFC-MLD Health states (1-6) and cognitive impairment sub-states (Normal function to significant cognitive impairment) were reported.	In interviews, members of the UK general public were asked to complete visual analogue scale (VAS) and time trade-off (TTO) assessment in-order to elicit utility values for Late Infantile and juvenile health states defined with input from clinical experts and patient groups. The interviews were conducted in two stages; in the first round of interviews [redacted] participants evaluated infantile health states. In the second round of interviews, a new set of [redacted] participants evaluated the juvenile health states.	Results are provided in Table C29	Consistency with reference case: The utility values reported are consistent with the reference case in as far as the use of the EQ-5D-5L instrument and this was elicited from members of the general public. Therefore these values would be expected to reflect the preferences of the UK general public. Appropriateness for cost-consequence

Study	Description of population and recruitment method	Country	Sample size and response rate	Intervention and comparator	Description of health states and adverse events	Methods of elicitation and valuation	Results	Appropriateness of study for cost-effectiveness evaluation
								model: The utility values are relevant to the cost-effectiveness model given the consistency of the values with the reference case

ABBREVIATIONS: MLD: Metachromatic Leukodystrophy; EQ-5D-5L: EuroQol 5 dimensions 5 levels questionnaire; TTO: Time Trade Off; VAS: Visual Analogue Scale.

Source: (Nafees et al., 2020 Unpublished)

10.4.3 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable as no studies identified by the literature search.

10.5 Adverse events

10.5.1 Please describe how adverse events have an impact on HRQL.

The safety findings following treatment with OTL-200 are consistent with what would be expected in patients with MLD and who have undergone busulfan conditioning and subsequent haematological reconstitution. No treatment related serious adverse events were observed in the clinical trials. In addition most of the adverse events were temporal and resolved spontaneously. As such, adverse events are not expected to have a significant impact on HRQoL.

As utility values were not collected during the clinical trials, direct estimates of the effect of the AEs on quality of life are not available.

10.6 Quality-of-life data used in cost-effectiveness analysis

10.6.1 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Utility values used in the base-case of the cost-effectiveness analysis are summarised in Table C29. All values were obtained from the utility study commissioned by Orchard Therapeutics. The utility values are consistent with the reference case as they were elicited from members of the general public using the TTO method with vignettes designed with input from clinical experts and patient groups. Therefore, it is justified to use these values in the cost-effectiveness analysis as they reflect the preferences of the UK general public.

Table C28: Summary of quality-of-life values for cost-effectiveness analysis

	Health States	Utility
Late Infantile	GMFC 1	[redacted]
	GMFC 2	[redacted]
	GMFC 3	[redacted]
	GMFC 4	[redacted]
	GMFC 5	[redacted]
	GMFC 6	[redacted]
Early Juvenile	GMFC1 + normal cognition	[redacted]
	GMFC2 + normal cognition	[redacted]
	GMFC3 + normal cognition	[redacted]
	GMFC4 + normal cognition	[redacted]
	GMFC0 +moderate cognitive impact	[redacted]
	GMFC1 +moderate cognitive impact	[redacted]
	GMFC2 +moderate cognitive impact	[redacted]
	GMFC3 +moderate cognitive impact	[redacted]
	GMFC4 +moderate cognitive impact	[redacted]
	GMFC5 +moderate cognitive impact	[redacted]
	GMFC6 +moderate cognitive impact	[redacted]
	GMFC0 + severe cognitive impact	[redacted]
	GMFC1 + severe cognitive impact	[redacted]
	GMFC2 + severe cognitive impact	[redacted]
	GMFC3 + severe cognitive impact	[redacted]

	GMFC4 + severe cognitive impact	[redacted]
	GMFC5 + severe cognitive impact	[redacted]
	GMFC6 + severe cognitive impact	[redacted]

10.6.2 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The utility values used in the cost-effectiveness model was obtained from the utility study described in Section 10.4.2. Clinical experts and patient groups informed the development of the health states vignettes as part of the utility study to elicit societal preference values associated with MLD in the UK. See the utility study report for further details (Nafees et al 2020).

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Healthcare professionals from the three paediatric LSD centres where MLD is managed were identified and interviewed. A total of n=6 paediatric consultants in metabolic disorders with experience of treating patients with either Late Infantile, juvenile or adult forms of MLD and n=1 clinical neuropsychologist with experience of assessing the cognitive performance of patients with MLD in the UK.

Two rounds of interviews were conducted with healthcare professionals. The first round of interviews was conducted with three clinicians to review the draft vignette for the Late Infantile MLD health states and provide feedback on the descriptions. Following these interviews, the health states were amended in line with the feedback provided and the revised drafts were sent to the healthcare professionals to ensure accuracy. Feedback on these health states was provided by email by two clinicians. A second round of interviews was conducted with two clinicians and one neuropsychologist who did not take part in the first round of interviews, to review and provide feedback on the vignettes for the juvenile MLD health states. (Nafees et al., 2020 Unpublished)

The values obtained from members of the general public using the validated vignettes, were then presented to the clinical experts in an advisory board meeting, who confirmed that these results represented clinical reality.

10.6.3 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Health-related quality of life is assumed to stay constant within individual health states.

A description of patient experience in each of the health states is provided in the vignettes that were prepared for each health state and validated by clinical experts. See Appendix C for further details.

10.6.4 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects identified in the literature or clinical trials were excluded from the analysis.

10.6.5 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The utility study (Nafees et al., 2020 Unpublished) was designed to generate utilities specific for the health states in the cost-effectiveness model. No adjustments were made for baseline utility.

10.6.6 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant over time within each health state as defined by motor and cognitive level. The HRQL will decline as the motor and cognitive levels become more severe.

10.6.7 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

HRQL values obtained from the utility study were not amended.

Treatment continuation rules

10.6.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed?

A treatment continuation rule was not considered since OTL-200 is a one-time treatment. No data exist on the safety and efficacy associated with repeat treatments.

Section D — Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

Summary:

- A de *novo* cost-effectiveness analysis of treatment with OTL-200, in comparison to best supportive care (BSC), was conducted for patients with Late Infantile (LI) or Early Juvenile (EJ) metachromatic leukodystrophy (MLD), in line with the NICE scope and interim methods for manufacturers and sponsors.
- A partitioned survival model was developed to track the progression of patients through seven health states based on the GMFC-MLD gross motor classification scale and key cognitive sub-states.
- A number of key assumptions were made related to the duration of clinical impact of OTL-200, MLD patient progression between GMFC-MLD and cognitive stages, and time to engraftment of OTL-200. These assumptions were further validated by expert clinical opinion or sourced from a structured expert elicitation process. The impact of these assumptions was also explored in several sensitivity analyses.
- Transition probabilities for the BSC arm were based on patient-level data from the OSR-TIGET natural history study, published literature and expert clinical opinion. Transition probabilities for the OTL-200 arm were based on the post-hoc analysis of the indicated population from the integrated data-set (as described in Section 9).

- Health utilities were derived from a Time Trade-Off (TTO) study in which vignettes in the form of health state descriptions representing components of motor and cognitive function were developed for LI and EJ patient populations, validated by clinical experts, and shared with 100 members of the general population in the UK into order to determine population preferences.
- Costs and resource use were identified through a structured expert elicitation process, and were implemented from an NHS/PSS perspective. Wherever cost information was not available, expert clinical opinion was used to inform the assumptions used for these inputs.
- For the combined MLD population (comprising all variants within the indication: PS LI, PS EJ and ES EJ), the base case analysis indicated that OTL-200 is associated with incremental gains of [redacted] QALYs and [redacted] life years versus BSC (at a discount rate of 1.5%). The corresponding base case ICER is [redacted] per QALY gained for OTL-200 versus best supportive care based on the PAS price.
- A number of scenario and sensitivity analyses have been conducted to assess the impact on the base case ICER.
- Scenario analyses included varying the parameter values for the discount rate, full-responder status, progression modifiers, caregiver disutlities, distributions of the underlying MLD disease cohorts in the combined population, and alternative natural history data sources. The majority of the scenario analyses demonstrated similar conclusions to the base case analysis, with ICERs at the PAS price in the range of £[redacted] to £[redacted] per QALY gained versus BSC.
- Subgroup analyses of each of the underlying disease variants (PS LI, PS EJ and ES EJ) indicated that OTL-200 was cost-effective in the pre-symptomatically treated population (determining ICERs of [redacted] per QALY gained for PS LI and [redacted] per QALY gained vs BSC for PS EJ), and also in the ES EJ population with an ICER of [redacted] per QALY gained vs BSC at the PAS price of OTL-200

- Deterministic sensitivity analyses, in which each parameter value was varied by ±20%, determined the main driver on the base case ICER to be drug cost, followed by the natural history rates of transition from GMFC-MLD 6 to death for LI and EJ.
- Probabilistic sensitivity analysis found the analyses performed to be robust, with values generated through this analysis aligning closely with the deterministic base case values.
- In summary, the cost-effectiveness analysis presents a robust evaluation, finding OTL-200 to offer significant benefits to all patients across the full indication.
- The key areas of uncertainty in the model with a significant impact on the cost-effectiveness are: (i) proportion of ES EJ Partial Responder OTL-200 patients stabilising at GMFC 2; (ii) the percentage of OTL-200 PS EJ that are full responders; and (iii) the percentage of OTL-200 PS LI that are full responders; emerging evidence from the ongoing clinical trials and post-marketing authorisation long-term follow-up of study should help resolve these uncertainties.
- With the advent of OTL-200, a potentially life-saving treatment for MLD with optimal clinical benefit when provided pre-symptomatically, the need for newborn screening to diagnose MLD will likely increase the proportion of pre-symptomatically diagnosed and treated MLD patients. Given that OTL-200 is the most cost-effective in the PS LI and PS EJ population, this future paradigm will likely improve the cost-effectiveness of OTL-200.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3

Health economic data were identified using the broad search strategy outlined in the HRQL studies Section 10.1.5.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

Articles identified from the SLR were included if they met the eligibility criteria presented in **Error! Reference source not found.**.

Table D1: Selection criteria used for health economic studies

Inclusion criteria	

Population	Patients with early-onset metachromatic leukodystrophy (MLD), i.e. diagnosed aged ≤ 17yrs[7].
	Subgroups of interest within the main population included:
	• Symptomatic MLD
	• Pre-symptomatic MLD
	• Late Infantile MLD
	• Juvenile MLD
	  ○ Early Juvenile
	  ○ Late Juvenile
	Where populations included a mixed age group including patients with onset of disease >17yrs, studies were only included if data were reported separately for those with early-onset disease (i.e. symptoms appearing ≤ 17yrs).

Interventions	The intervention of interest was *ex-vivo* autologous lentiviral gene therapy, specifically OTL-200. The following were included: • OTL-200 treatment arms in single arm studies • OTL-200 treatment arms in RCTs and cohort studies making a comparison with a relevant comparator treatment of interest. Comparator treatments of interest were: • Standard care/best supportive care/usual care* • Allogeneic haematopoietic stem cell transplantation (HSCT)[8] The following were included: • Comparator treatment arms in single arm studies Comparator treatment arms in RCT and cohort studies comparing the comparator treatments with each other or against the intervention of interest (i.e. OTL-200)

Outcomes	Economic or utility studies reporting at least one of the following specific outcomes relevant to the NICE scope
	
	Health related quality of life (HRQoL):
	• Mean change (SD) from baseline in Caregiver Observed Metachromatic Leukodystrophy Functioning and Outcomes Reporting Tool (COMFORT)
	• Mean change (SD) from baseline in the (EQ-5D)
	
	Economic:
	• Health-related quality of life
	• Utilities
	• Costs and use of resources
	• For economic evaluations:
	  ○ Location of study
	  ○ Summary of model and comparators
	  ○ Patient population (key characteristics, average age)
	  ○ Costs (intervention and comparator)
	  ○ Patient outcomes (clinical outcomes, quality adjusted life expectancy (QALYs), life expectancy)
	  ○ Results (annual cost savings, annual savings per patient, incremental cost per QALY (ICER))

[7] At the time of initiating the SLR, the draft indication still included late juvenile MLD patients, hence why the SLR includes evidence from MLD children up to 17 years and those treated with allogeneic HSCT. The current indication with positive CHMP opinion on 15th October 2020, no longer includes late juvenile patients

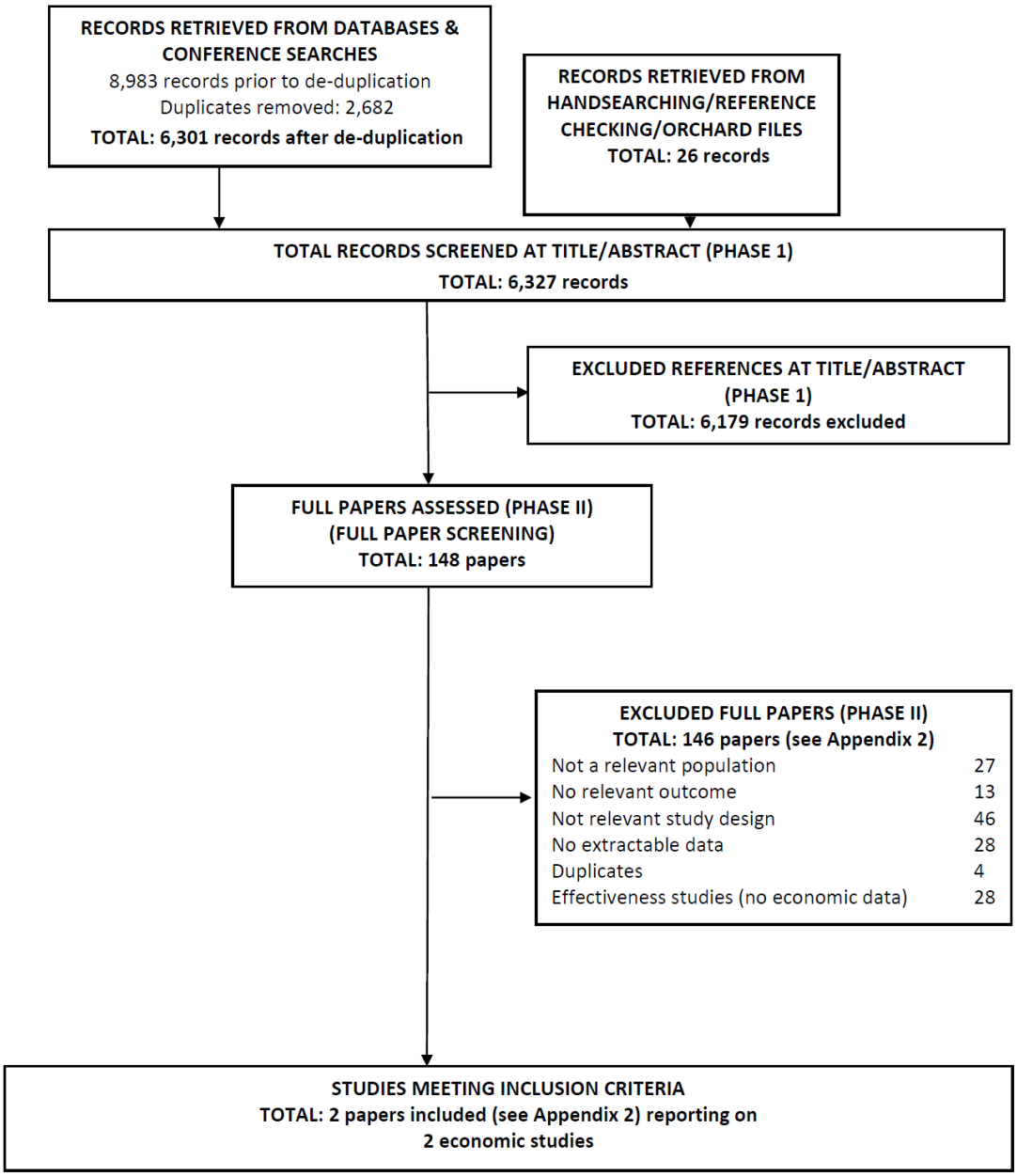
[8] At the time of initiating the SLR, the draft indication still included late juvenile MLD patients, hence why the SLR included allogeneic HSCT as a comparator given its use in this subset of patients. As the current indication with positive CHMP opinion on 15th October 2020, no longer has late juvenile patients, allogeneic HSCT will not be a comparator for OTL-200 given its not a treatment option in this patient group

Study design	Any type of economic evaluation (cost-effectiveness analysis (CEA), cost only comparison, budget impact analysis (BIA) or cost of illness (COI) study)
Language restrictions	Searches were not limited by language.
Search dates	Databases from database inception to May 2020. Conferences 2018-2020. ClinicalTrials.gov (NIH): Up to 19 May 2020. Orphanet Clinical trials search (Internet): up to 04 June 2020.
Exclusion criteria	
Population	Studies not reporting data on patients with early-onset metachromatic leukodystrophy (MLD), i.e. diagnosed aged ≤ 17yrs, including those where populations included a mixed age group including patients with onset of disease >17yrs, and data were not reported separately for those with early-onset disease (i.e. symptoms appearing ≤ 17yrs). Studies with ≤ 5 participants.
Interventions	Studies not reporting data on the listed interventions or comparators.
Outcomes	All other outcomes. Vector clone number (VCN) and % lentivirus (LV) + clone are outcomes only relevant for OTL-200 gene therapy, these will not be recorded as key outcomes.
Study design	All other study designs including, but not limited to, case reports, cross-sectional studies, animal studies or biochemical or cellular level investigations.
Language restrictions	Searches were not limited by language.
Search dates	None.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format

The electronic database searches identified a total of 8,983 records. After screening of titles and abstracts, 148 relevant citations were selected. Following a detailed evaluation of the full texts of these articles, all but 2 of the records were excluded as they did not meet the review inclusion criteria. Both studies were caregiver burden studies (Pang et al., 2020, Eichler et al., 2016). One of these studies provided utility estimates for caregivers. There were no studies of cost effectiveness analysis (CEA), cost only comparison, budget impact analysis (BIA) or cost of illness (COI) were identified. Where resource use was identified in these studies it was not expressed in monetary terms, except in the case of indirect carer costs reported in Pang et al 2020.

Figure D1: PRISMA flow diagram of economic SLR



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

No relevant studies were identified.

11.2.2 Provide a complete quality assessment for each health economic study identified.

This section is not applicable as no relevant studies were identified.

12 Economic analysis

Section 12 requires the sponsor to provide information on the *de novo* cost-effectiveness analysis.

The *de novo* cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The cost-effectiveness analysis of OTL-200 is conducted within its licensed indication. The patient groups included in the cost-effectiveness analysis are children less than 7 years of age with genetically confirmed Late Infantile or Early Juvenile metachromatic leukodystrophy (MLD), based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles. The modelled population consists of a combination of the following three patient groups:

1. Pre-symptomatic Late Infantile (PS LI): Children with a confirmed diagnosis of Late Infantile MLD without clinical manifestations of the disease
2. Pre-symptomatic Early Juvenile (PS EJ): Children with a confirmed diagnosis of Early Juvenile MLD without clinical manifestations of the disease
3. Early-symptomatic Early Juvenile (ES EJ): Children with Early Juvenile MLD have early clinical manifestations of the disease, with the ability to

walk independently (GMFC-MLD ≤ 1) and before the onset of cognitive decline (IQ ≥ 85).

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

Technology

OTL-200 is an *ex vivo* genetically modified autologous CD34+ haematopoietic stem and progenitor cell gene therapy administered as a dispersion for infusion. It should be administered as a one-time treatment administered via a single IV infusion with a myeloablative conditioning regimen. There are no required 'stopping rules' and the effects are estimated to be life-long.

Comparator

In line with the NICE scope, BSC was used as the comparator in the cost-effectiveness analysis. Haematopoietic stem cell transplant (HSCT) was not considered a valid comparator for this HST appraisal for the following reasons:

i) Feedback from clinical experts is that allogeneic HSCT is not routinely used in patients with Late Infantile or Early Juvenile MLD as the potential risks would outweigh any potential benefits.

ii) Evidence from several publications have indicated poor outcomes for HSCT in patients with LI or EJ MLD (Tan et al., 2019, van Rappard et al., 2015) based on the following rationale:

- The replacement of resident tissue macrophages and microglia populations by donor-derived progeny may be too slow to stop or slow down the rapid progression of disease (Peters and Steward, 2003, Krägeloh-Mann et al., 2013, Solders et al., 2014).
- The engrafted microglial cells following allogeneic HSCT produce ARSA enzymes at normal levels which are insufficient to produce cross-correction of the defective neuronal and glial cells within the brain (Wolf et al., 2020).

- The use of HSCT in juvenile patients carries a risk of accelerating disease progression compared to best supportive care in some patients (the exact reason for this is unknown) (Beschle et al., 2020).
- Allogeneic HSCT is associated with a significant risk of death as well as debilitating complications such as Graft vs Host disease (GvHD) (Groeschel et al., 2016).

(iii) At the time of the scoping workshop, the provisional indication of OTL-200 included patients with late juvenile MLD. Based on clinical opinion and evidence from the scientific literature, allogeneic HSCT is regarded as a potential treatment option for patients for this variant). However, the CHMP approved indication for OTL-200 no longer includes the late juvenile MLD variant and hence has not been modelled in this cost-effectiveness analysis.

BSC aims to manage disease complications and support any residual quality of life as far as possible, but does not target the root cause of the progressive motor and cognitive decline or halt disease progression.

Current BSC therapies include physical therapy, pain management, management of skeletal deformity, respiratory physiotherapy, anti-convulsant drugs to control seizures, and anti-psychotic medications, as well as enteral nutrition through a feeding tube in cases of dysphagia, and mechanical ventilatory support.

- The data source for BSC are subjects from the OSR-TIGET natural history (NHx) study, who were age and disease subtyped matched to patients from the OTL-200 clinical trials. The OSR-TIGET NHx study was carried out by the San Raffaele Telethon Institute for Gene Therapy (TIGET) in Italy, and was performed in conjunction with the OTL-200 clinical development programme enrolling patients since 2004. The OSR-TIGET NHx study consists of a cohort of 31 early-onset MLD patients (19 LI and 12 EJ) managed with best supportive care (BSC) in Italy. Thirty-five percent (11 out of 31) of the OSR-TIGET natural history study patients were matched siblings with OTL-200 treated clinical trial patients.

- For comparison to pre-symptomatic OTL-200 patients, natural history patients enter the model prior to symptom onset using adjustments derived from published literature and validated clinical assumptions.

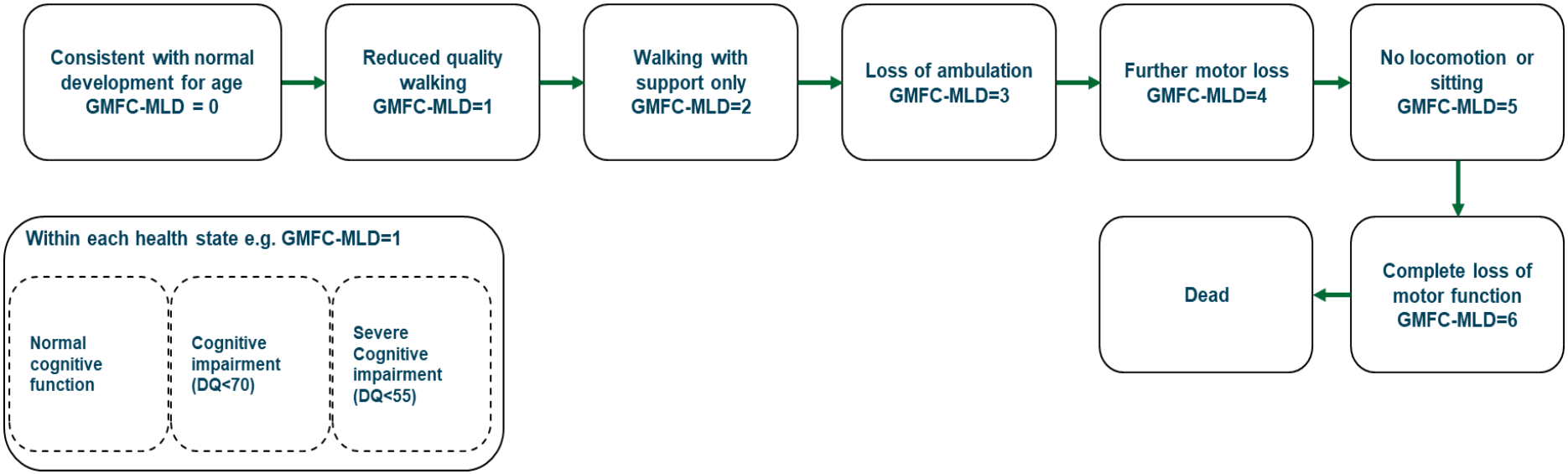
There are currently no approved, effective treatments for MLD.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen

The cost-effectiveness model is a seven-state partitioned survival model. The structure of the model is shown in Figure D2. The partitioned survival model approach has been used in a number of other positively recommended NICE HST assessments and is deemed to be a reliable method for modelling diseases with motor function progression involvement (Landfeldt et al., 2017, National Institute for Health and Care Excellence, 2015).

Figure D2: Model schematic



Health states

The cost-effectiveness model, (depicted in Figure D2) is a seven-state partitioned survival model constructed from a UK NHS / PSS perspective. In order to accurately reflect the clinical course of disease progression in MLD, seven health states were defined based on natural history data and advice from clinical experts. The model health states track the progression of the natural history of MLD, using the following constructs:

- Clinically validated MLD gross motor function classification (GMFC-MLD) stage
- In EJ MLD patients, cognitive function is also used as a modifier for each state, measured using the developmental quotient performance scale
- Time to death

For patients treated pre-symptomatically, the model includes one health state (GMFC-MLD 0) that reflects patients whom have not yet experienced motor function decline and are still developing within a broad range of normal development. Once clinical manifestations of the disease have occurred, individuals may transition through GMFC-MLD levels 1–6, reflecting the progressive decline and loss of motor function ability.

In PS LI MLD, cognitive decline occurs at a similar rate to motor function decline. In contrast, for PS EJ and ES EJ MLD, cognitive decline can occur before or after motor function loss. For each of the GMFC-MLD stages in EJ patients, three cognitive sub-states were also included to reflect the cognitive progression of MLD, and hence enable the capture of the combined effects of cognitive decline and motor function loss on patients. Additionally, the GMFCMLD 6 health state captures the portion of patients that will require in-patient hospitalisation. Whilst the health states are broadly defined by the motor function and cognitive status, each health state also captures the likely associated symptoms and complications of MLD.

The time horizon for the model is a lifetime horizon with outcomes measured as Quality Adjusted Life Years (QALYs).

The combined model population presented in the base case results is a weighted average of each eligible disease cohort (i.e. PS LI, PS EJ, ES EJ). Proportions of the combined MLD model population (presented in Table D2) were derived from a convergence of evidence from epidemiological sources and the structured expert elicitation process. (Orchard Data on file, 2020)

Table D2: MLD Combined eligible patient population breakdown by disease cohort

MLD Disease Cohort	Percentage of Combined Cohort
PS LI	[redacted]
PS EJ	[redacted]
ES EJ	[redacted]

Transitions

At model entry in the base case, the overall cohort is distributed across PS LI, PS- J and ES EJ subgroups reflecting the expected population that will receive treatment for MLD disease. This proportion of the expected population by variant was validated by clinical experts and is detailed in Table D3**Error! Reference source not found.**. The age at model entry for each of the disease variants is based on the mean age at treatment in the OTL-200 clinical trial (PS EJ and ES EJ) or the earliest age at which the GMFC-MLD score can be used (PS LI). The PS LI model begins as 18 months of age because GMFC-MLD scores are validated for use in patients older than 18 months of age as GMFC-MLD 0 is based on an un-impacted patient's ability to achieve walking without support within the range of normal development.

Table D3: Age and health state of MLD patients at model entry

Disease Variant	GMFC-MLD Stage at Model Entry	Patient Age at Model Entry
PS LI	100% GMFC-MLD 0	18 months
PS EJ	100% GMFC-MLD 0	45 months
ESEJ	40% GMFC-MLD 0 60% GMFC-MLD 1	80 months

At baseline, all pre-symptomatic patients (i.e. PS LI and PS EJ) are in GMFC-MLD 0, where they remain until they first experience clinical onset of disease, defined by progression beyond GMFC-MLD 0. Early symptomatic patients (i.e. ES EJ only) enter the model either in GMFC-MLD 0 (40% of patients) or in GMFC-MLD 1 (60% of patients) based on the distribution of OTL-200 treated patients at entry into the Orchard Therapeutics clinical trials.

The model uses monthly model cycles to capture rapid changes in MLD gross motor function and cognitive function progression.

Best supportive care (BSC) transitions

In the BSC arm at each cycle, patients can transition into the next GMFC-MLD health state, stay in the same health state, or transition to death. Individuals can only progress to the next GMFC-MLD stage (e.g. from GMFC-MLD 1 to GMFC-MLD 2) and cannot improve (e.g. patients cannot transition from GMFC-MLD 1 to GMFC-MLD 0) i.e. there are no backward transitions. To estimate the monthly probability of transitioning to each subsequent health state, the model includes 'mean time to transition' inputs that are adjustable for each state, for example, the user can update the mean time between entering GMFC-MLD 2 and entering GMFC-MLD 3, which will adjust the underlying transition probabilities. The default amount of time a patient spends in each health state is derived from data from the age and disease subtype matched natural history cohort which was used as the comparator for the OTL-200 trials, where available, and supplemented with published literature and expert clinical opinion. Multiple options are provided in the model as well

as customisable user input options. Mean time to transition values for each modelled disease variant are presented in Table D4 and Table D5.

Table D4: BSC: Modelled LI 'Mean time to transition' inputs

Model Transition	Mean time to transition: TIGET Historical Control	Mean time to transition: Elgun, 2019	Mean time to transition: Kehrer, 2011
GMFC-MLD 0 to 1	[redacted]	10 months	10 months*
GMFC-MLD 1 to 2	[redacted]	6 months	8 months
GMFC-MLD 2 to 3	[redacted]	2 months	4 months
GMFC-MLD 3 to 4	[redacted]	2 months	4 months
GMFC-MLD 4 to 5	[redacted]	2 months	4 months
GMFC-MLD 5 to 6	[redacted]	2 months	2 months
GMFC-MLD 6 to Death	[redacted]	57 months**	57 months**

Note: GMFC-MLD 2 to 3, GMFC-MLD 3 to 4 and GMFC-MLD 4 to 5 calculated by evenly distributing the months from GMFC-MLD 2 to 5.
*Not reported in trial/publication, used time at entry into GMFC-MLD 1 reported in Elgun, 2019 as proxy
**Not reported in publication, used value from Orchard Therapeutics clinical trial as proxy

Table D5: BSC: Modelled EJ 'Mean time to transition' inputs

Model Transition	Mean time to transition: TIGET Historical Control	Mean time to transition: Elgun, 2019	Mean time to transition: Kehrer, 2011
GMFC-MLD 0 to 1	[redacted]	-	-
GMFC-MLD 1 to 2	[redacted]	10 months	27 months
GMFC-MLD 2 to 3	[redacted]	4 months	2 months
GMFC-MLD 3 to 4	[redacted]	4 months	2 months
GMFC-MLD 4 to 5	[redacted]	4 months	2 months
GMFC-MLD 5 to 6	[redacted]	7 months	12 months
GMFC-MLD 6 to Death	[redacted]	-	-

Note: GMFC-MLD 2 to 3, GMFC-MLD 3 to 4 and GMFC-MLD 4 to 5 calculated by evenly distributing the months from GMFC-MLD 2 to 5.
* Not derived from clinical data. Assumed to be 58.3 months to align PS-EJ and ES-EJ cohorts using the age and GMFC-MLD distribution at treatment from patients in the OTL-200 clinical trial.
**Not reported in publication, used value from Orchard Therapeutics clinical trial as proxy

Transition probabilities between health states were originally calculated based on the methodology published by Landfeldt et al., 2017 for Duchene Muscular Dystrophy (9), due to the similar progressive nature of the disease. However, the transition probability formulae provided by the ERG have been used to estimate transition probabilities with a constant hazard between each of the GMFC-MLD stages 1–6. In the economic model the '1-(1/mean time in state)' transition rate provided by the ERG can be converted into the transition probability using the following formula:

$$Tp_{cycle\ length} = 1 - \exp\left(-(transition\ rate) * cycle\ length\right)$$

Thus, the following formula was applied to calculate the transition probability assuming a constant hazard when using the mean time in state input value:

$$Tp_{cycle\ length} = 1 - \exp\left(-\left(\frac{1}{mean\ time\ in\ state}\right) * cycle\ length\right)$$

In the OSR-TIGET natural history study, death from MLD is preceded by loss of all motor function (GMFC-MLD 6) (i.e. 100% of patients progress to GMFC-

MLD 6 before death). Therefore, it was assumed that transitions to death due to MLD is only possible from GMFC-MLD 6. This assumption was validated with clinical experts who confirmed that patients will progress through all GMFC-MLD stages prior to death due to MLD. In the revised analysis, a different approach was adopted for the transition probability from GMFC-MLD 6 to death as suggested by the ERG. Rather than model a constant hazard rate from GMFC-MLD 6 to death based on the mean time from GMFC 6 to death, GMFC 6 survival utilises parametric curves fitted to the LI and EJ natural history data to model survival beyond the trial period. Modelling mortality in GMFC-MLD 6 with increasing hazards allows the model to incorporate all patients (i.e., those lost to follow-up/censored) in the survival calculations. Furthermore, the increasing hazards model supports the natural history of the disease in that the likelihood of death occurring in GMFC-MLD 6 increases over time (see Appendix F for further information).

To capture all-cause mortality, general population mortality was applied to GMFC-MLD 0 through GMFC-MLD 6.

OTL-200 transitions

OTL-200 patients have the potential to experience life-long benefits of treatment. Clinical experts assert that these benefits include possible prevention, delay, or slowing of clinical manifestation of disease. These benefits will vary across individuals, who may be classified as “full responders” or “partial responders” depending on their response to treatment (see Table 5 for breakdown). Patients were considered full-responders if they were pre-symptomatic at the time of treatment and demonstrated broad stabilisation throughout the clinical trial follow-up period (i.e. did not progress past GMFC-MLD 0), illustrating that they had received treatment before irreversible damage had taken place. Patients were considered partial responders if they were treated pre-symptomatically and continued to progress beyond GMFC-MLD 0 during the trial period (i.e. GMFC-MLD 2 to GMFC-MLD 6 or death) or were symptomatic at the time of OTL-200 treatment. The criteria for full and partial responders were confirmed by clinical key opinion leaders.

Table D6: Model Base case full- and partial-responder breakdown by disease variant

Responder Status	Disease Variant		
	PS LI	PS EJ	ES EJ
Percentage of Full Responders	[redacted]	[redacted]	[redacted]
Percentage of Partial Responders	[redacted]	[redacted]	[redacted]

To capture the potential benefits of treatment, the OTL-200 arm of the model includes a number of clinical parameters that reflect halting or slowing of disease progression:

1. Time to progression parameter
2. Stabilisation parameters
3. Progression modifier parameters
4. Time to engraftment parameter
5. Cognitive sub-state distributions

A detailed explanation of each clinical parameter is provided below.

1. Time to progression Parameter

The 'time to progression' parameter was implemented for OTL-200 full responders to simulate the potential impact of OTL-200 treatment preventing onset of clinical symptoms (that is, in full-responders it is assumed there is potential for the prevention of disease onset). OTL-200 would prevent MLD disease progression in full-responder patients and these patients would remain in GMFC-MLD 0 for the duration of the 'time to progression' value. For the model base case, the 'time to progression' parameter was set at 100 years to simulate a lifetime duration of effect of OTL-200 treatment, which was validated by clinical experts.

2. Stabilisation parameters

Based on data from the clinical trials, a proportion of OTL-200 treated partial-responder patients would stabilise (i.e. prevent continued MLD disease

progression) in GMFC-MLD 1 and 2 after an initial disease progression. Three parameters were generated to simulate 'stabilisation' in PS LI, PS EJ and ES EJ partial responder patients:

- Percentage of partial-responders stabilising: The proportion of partial-responders that will experience 'stabilisation' rather than a protracted, continued MLD disease progression. For the base case, this parameter was based on data from the clinical trials for each specific disease variant (i.e. PS LI, PS EJ and ES EJ).
- GMFC-MLD stage at stabilisation: Simulating the GMFC-MLD stage where patients would 'stabilise' and remain for the duration of stabilisation. Based on an evaluation of the clinical trial data, the data show that of the patients who are not full responders, a large proportion will stabilise at either GMFC-MLD 1 or 2, and a small proportion of partial responders progress through the MLD disease states but at a much slower rate than best supportive care/natural history patients.
- Duration of stabilisation: Simulating the length of time that the proportion of partial-responder patients would experience 'stabilisation'. Based on clinical expert advice gathered in the structured expert elicitation process (Orchard Data on file, 2020), 'stabilised' patients from the PS LI, PS EJ and ES EJ cohorts were assumed to prevent further MLD disease progression for a lifetime horizon (100 years).

Stabilisation parameter values for the model base case are presented in Table D7 for each disease variant and were obtained from a mixture of OTL-200 clinical trial data and from clinical experts as part of the SEE.

Table D7: Model base case stabilisation parameters for OTL-200 partial responders by disease variant

Stabilisation parameter	Disease variant		
	PS LI	PS EJ	ES EJ
Percentage of partial responders stabilising	[redacted]	[redacted]	[redacted]
GMFC-MLD stage at stabilisation	GMFC-MLD 2	GMFC-MLD 2	GMFC-MLD 2
Duration of stabilisation	100 years	100 years	100 years

3. Progression modifier Parameter

OTL-200 treated patients are also assumed to spend longer in each subsequent health state, based on clinical expert advice that treated patients have the potential to slow disease progression (“sliding down the hill” instead of “falling off a cliff”). The 'progression modifier' parameter is used in the model to simulate protraction of disease progression compared to the natural history. For each GMFC-MLD stage, modifiable 'progression modifier' inputs were used to calculate time to transition rates of progression that simulated stabilising or slowing of disease progression for OTL-200 treated patients. OTL-200 time to transitions were calculated by multiplying the 'progression modifier' value by the natural history time to transition for each GMFC-MLD stage.

For the PS LI and PS EJ cohorts, the 'progression modifiers' were obtained using two different approaches.

(i) The first approach (termed calculation method) involved deriving a ratio comparing the average time from GMFC-MLD 2 to GMFC-MLD 5 from the OSR-TIGET natural history- trial (among a combined dataset of the LI and EJ cohorts) and OTL-200 indicated population (among a combined dataset of the LI and EJ cohort partial responders). It should be noted that rate of disease progression in the rapid disease progression phase (GMFC-MLD 2 to 5) is similar irrespective of disease variant (Harrington et al., 2019). To avoid overestimating the impact of treatment, only OTL-

200 partial-responders i.e. the subset of OTL-200 patients who experienced disease progression (worsening of GMFC-MLD state) were used in estimating the 'progression modifier'. These progression modifiers were applied to all GMFC-MLD transitions except the transition from GMFC-MLD 6 to death. In addition, following advice from the ERG, the progression modifiers calculated for transitions have been conservatively set at between 0.69 and 0.96 for between GMFC 0 to 1, rather than 3.21, and between 0.87 to 1.46 for GMFC 1 to 2 to provide disease progression equivalent to natural history. This is based on the progression rate observed in the clinical trial patients compared to the natural history patients over this time frame. 'Progression modifier' parameters and mean times to transition for each disease variant are presented in Table D8, Table D9 and Table D10.

(ii) The second approach involved obtaining “progression modifiers” from a structured expert elicitation process. These values were examined in a scenario analysis (Scenario description in Table D28 and results in Table D45).

It was not possible to use the calculation method to estimate the value of the progression modifier for the ES EJ cohort, due to the paucity of data and small sample size, Therefore 'progression modifiers' were obtained from clinical experts via structured expert elicitation only. (Orchard Data on file, 2020)

Table D8: PS LI mean time to transition values

Transitions	Mean time to transition (months)				
	BSC: OSR-TIGET Natural history	Progression Modifiers (Calculation)	OTL-200 Mean Time (Calculation)	Progression Modifiers (SEE)	OTL-200 Mean Time (SEE)
from 0 to 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 1 to 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 2 to 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 3 to 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 4 to 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 5 to 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 6 to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Calculation values used for base case, SEE values included for scenario analysis. SEE progression modifier value for transition from GMFC-MLD 0 to 1 was not collected and assumed to be identical to the calculated value. SEE progression modifier values for transition from GMFC-MLD 5 to 6 and GMFC-MLD 6 to death were not collected and assumed to be equal to natural history.
SEE: Structured expert elicitation; Calculation: Calculated values from GMFC-MLD 2 to 5 for the indicated population.

Table D9: PS EJ mean time to transition values

Transitions	Mean time to transition (months)				
	BSC: OSR-TIGET Natural history	Progression Modifiers (Calculation)	OTL-200 Mean Time (Calculation)	Progression Modifiers (SEE)	OTL-200 Mean Time (SEE)
from 0 to 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 1 to 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 2 to 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 3 to 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 4 to 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 5 to 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 6 to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Calculation values used for base case, SEE values included for scenario analysis. SEE progression modifier value for transition from GMFC-MLD 0 to 1 was not collected and assumed to be identical to the calculated value. SEE progression modifier values for

transition from GMFC-MLD 5 to 6 and GMFC-MLD 6 to death were not collected and assumed to be equal to natural history.
SEE: Structured expert elicitation; Calculation: Calculated values from GMFC-MLD 2 to 5 for the indicated populations

Table D10: ES EJ mean time to transition values

Transitions	Mean time to transition (months)		
	BSC: OSR-TIGET Natural history	Progression Modifiers (SEE)	OTL-200 Mean Time (SEE)
from 0 to 1	[redacted]	[redacted]	[redacted]
from 1 to 2	[redacted]	[redacted]	[redacted]
from 2 to 3	[redacted]	[redacted]	[redacted]
from 3 to 4	[redacted]	[redacted]	[redacted]
from 4 to 5	[redacted]	[redacted]	[redacted]
from 5 to 6	[redacted]	[redacted]	[redacted]
from 6 to death	[redacted]	[redacted]	[redacted]

Note: SEE progression modifier value for transition from GMFC-MLD 0 to 1 was not collected and assumed to be equal to natural history. SEE progression modifier values for transition from GMFC-MLD 5 to 6 and GMFC-MLD 6 to death were not collected and assumed to be equal to natural history. Calculation values not used for ES EJ cohort.
SEE: Structured expert elicitation.

4. Time to engraftment parameter

In the ES EJ model, the time required for OTL-200 to take effect post-treatment is captured by applying a 'time to engraftment' parameter based on clinical expert feedback that as patients were already symptomatic at the time of treatment, MLD disease progression will continue for ES EJ patients at the same rate as natural history until engraftment of the gene corrected stem cells occurs in the brain. The 'time to engraftment' parameter dictates the duration of time post-treatment before full- and partial-responders receive the benefits of OTL-200 treatment from the 'time to progression', 'stabilisation' and 'progression modifier' parameters. In the model, the 'time to engraftment' parameter only impacts the ES EJ patients because pre-symptomatic patients are assumed to experience engraftment prior to MLD disease onset. However, as stated above the progression modifiers calculated for transitions between GMFC 0 to 1, and 1 to 2 have been conservatively set at 1.00 rather

than 3.21 to provide disease progression equivalent to natural history. This is to account for any pre-engraftment progression in pre-symptomatic patients receiving OTL-200.

For the base-case, the 'time to engraftment' was valued at [redacted] months post-treatment for the ES EJ cohort, based on the time taken for ASRA enzymes to reach the required supraphysiological levels (i.e. confirming engraftment) as presented in [redacted]

Figure D3: [redacted]

5. Cognitive sub-state distributions

To reflect the cognitive decline that can occur before or after motor function loss in EJ patients, cognitive sub-states were developed for each GMFC-MLD stage. Cognitive sub-states were based on observed data, derived from Developmental Quotient — Performance (DQp) scores, and categorised into 3 groups that were considered clinically meaningful by clinical experts:

- Normal/mild cognition (DQp > 70)
- Moderately impaired cognition (70 ≤ DQp ≥ 55)
- Severely impaired cognition (DQp < 55).

For each EJ cohort (PS EJ BSC, ES EJ BSC, PS EJ Full-responders, PS EJ Partial-responders and ES EJ Partial-responders), patients were distributed into one of the three cognitive sub-states for each of the GMFC-MLD stages based upon the observed data for the cohort (via the Orchard Therapeutics clinical trial DQ performance data) and clinical expert feedback obtained via structured expert elicitation. Clinical experts also expected that cognitive loss could occur prior to gross motor decline (i.e. in GMFC-MLD 0). The GMFC-MLD 0 cognitive distributions were stratified into two groups:

- “GMFC-MLD 0: Before cognitive decline” to simulate the cognitive distribution of patients entering the model.
- “GMFC-MLD 0: After cognitive decline” to simulate the initial cognitive loss prior to gross motor function decline.

A “time until cognitive decline” parameter was included for each EJ cohort to simulate the length of time that would elapse before patients remaining in GMFC-MLD 0 would experience a cognitive decline (i.e. transition from “Before cognitive decline” to “After cognitive decline”).

At each cycle, the patients in each GMFC-MLD stage were distributed into the cognitive sub-states based on the cognitive distributions for the cohort (see Appendix D for cognitive distributions for each cohort). The cognitive sub-states were used to apply sub-state specific HRQoL utility scores associated with each GMFC-MLD stage. Cognitive sub-states are assumed to have no impact on survival or costs.

A summary of the modelled clinical benefits of OTL-200 is presented in Table D11 below.

Table D11: Summary of modelled clinical benefits of OTL-200 treated patients

	Full-Responders	Partial Responders
Classification Criteria	OTL-200 treated patients that do not progress beyond GMFC 0	OTL-200 treated patients that progress beyond GMFC 0 (in GMFC 1+) or are symptomatic at treatment
Modelled Benefit	Prevention of Disease Progression Retention of cognitive abilities	Protracted or stabilised/halted disease progression Retention of cognitive abilities
Applied Model Parameters	Time to progression Cognitive sub-state Time until cognitive decline Time to engraftment	Progression modifiers Stabilisation parameters Cognitive sub-states Time until cognitive decline Time to engraftment

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The cost-effectiveness modelling framework was conceptualised together with MLD clinical experts, and influenced by health economic models for similar rare genetic neuromuscular disorders, such as Duchene's muscular dystrophy, as there were no models currently developed for MLD. This progressive health state model framework (from consistent with normal development [GMFC-MLD 0] to complete loss of motor function [GMFC-MLD 6]), that extrapolates observed rates of progression from clinical data across the duration of the modelling period, is broadly aligned to the model structure evaluated by the NICE- HST and US ICER (Institute of Clinical and Economic Review) assessment of DMD therapies (Landfeldt et al., 2017, Institute for Clinical and Economic Review, 2019).

Prior to the development of disease-modifying therapies for MLD, disease progression was inevitable and irreversible. Once diagnosed, following a short period of developmental plateau, symptomatic patients would experience rapid, progressive deterioration and early mortality. Rapid progression typically beginning at the age of 18 months for Late Infantile patients and between 30 months and 6 years for Early Juvenile patients (Harrington et al., 2019).

With ex-vivo gene therapy, children with MLD in the Orchard Therapeutics clinical trials are observed to halt or stabilise slow down disease progression (i.e. retain cognitive and motor function), which correlates with improved functionality, HRQoL and survival. In patients treated pre-symptomatically, some patients ("full responders") are yet to experience clinical onset of disease such as motor function loss or cognitive issues.

Thus, the health economic model is designed to capture both the natural history of disease (progressive decline in untreated patients and partial responders) and the potential of ex-vivo gene therapy to prevent or delay disease onset, and slow or halt disease progression from both the motor and cognitive perspectives.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption

The model is underpinned by these foundational assumptions:

1. **Pre-symptomatic OTL-200 treated patients who are full responders will not develop clinical manifestations of MLD throughout their life**

   OTL-200 works to repopulate the brain with self-renewing gene corrected stem cells that are able to synthesize the missing ARSA enzyme thereby preventing the onset of clinical manifestations of the disease. The mutated ARSA gene is replaced and underlying disease mechanisms stopped, which results in the prevention loss of motor and cognitive function when patients are treated pre-symptomatically (i.e. before patients experience the onset of MLD symptoms/progression).

   Justification: The results of the OTL-200 clinical trials to date indicate that a one-time IV administration of OTL-200 at the therapeutic dose provides prolonged efficacy for durations of up to 7.5 years (up to 90 months) post gene therapy administration in LI patients and 6.55 years (up to 78.6 months) post gene therapy administration in EJ patients.

   In addition, based on the known mechanism of action and the self-renewing properties of hematopoietic stem cells, engrafted gene-

corrected stem cells will synthesise ARSA enzyme at supraphysiological levels throughout the lifetime of the patient. The enzyme is secreted into the extracellular matrix and taken up by surrounding cells leading to the intracellular breakdown of harmful sulfatides and preventing their accumulation; in turn, these actions on sulfatides prevent the processes that underlie the clinical manifestations and disease progression of MLD, namely brain and PNS demyelination, neurodegeneration and atrophy resulting in sustained prevention of MLD symptom onset. (Fischer et al., 2010)

Furthermore, the modelling complications regarding the assumptions of durability associated with adeno-associated virus gene therapies are not expected for the ex-vivo hematopoietic stem cell approach as the long term durability of efficacy of the HSC ex-vivo gene therapy is well established. (Fischer et al., 2010) For example, ADA-SCID patients treated with Strimvelis (an autologous HSC ex-vivo gene therapy) have been shown to remain event-free (i.e. symptom-free) after more than 19 years of follow-up.

2. **Pre-symptomatic or early symptomatic OTL-200 treated patients who are partial responders will have slower disease progression compared to natural history patients**

   OTL-200 can slow down of rate of MLD disease progression, resulting in long-term retention of motor and cognitive function when patients are treated symptomatically (where prevention of disease onset is not possible) or when treated pre-symptomatically and experiencing disease progression (possible due to onset of symptoms occurring prior to successful engraftment of gene corrected cells).

   Justification: The results of the OTL-200 clinical trials to date indicate that in some patients a one-time IV administration of OTL-200 at the therapeutic dose results in a slowing of disease progression in LI and EJ patients. The reason for why some patients would be full responders and others are partial responders is not fully understood, but may reflect the varying degrees to which engraftment of gene -corrected cells occurs in

patients, with full responders possibly having a greater concentration of engrafted cells compared to partial responders.

3. **A proportion of pre-symptomatic or early symptomatic OTL-200 treated patients who are partial responders will stabilise and halt disease progression at GMFC-MLD 2**

   OTL-200 can prevent further MLD disease progression in a proportion of partial-responder patients (i.e. pre-symptomatic or early symptomatic patients that have previously experienced MLD disease progression), resulting in long-term retention of motor and cognitive function.

   Justification: Based on data from the clinical trials and supported by clinical expert advice gathered in the structured expert elicitation process, a proportion of OTL-200 treated patients that progress to GMFC-MLD 1 and 2 may “stabilise” at GMFC-MLD 1 and 2 i.e. halt further disease progression for a lifetime. The rationale for disease stabilisation is that the initial progression could be solely because in some patients the development of clinical manifestations of the disease (for PS patients) or some disease progression for ES EJ may occur before successful engraftment of the gene-corrected stem cells. Once engraftment has occurred, the engrafted cells in these patients are able to release ARSA at sufficient rate and concentration to prevent further cell damage.

4. **In ES EJ patients there will be a delay for the clinical effects of OTL-200 to become apparent**

   OTL-200 requires some time for the effects to become apparent because of the time required for engraftment of the gene corrected cells.

   Justification: Based on clinical expert advice, MLD disease progression will continue for OTL-200 treated ES EJ patients at the same rate as natural history until engraftment of stem cells takes place in the brain. Given that pre-symptomatic patients will be treated prior to symptom onset, engraftment would also occur prior to symptom onset, so no observable delay would be required for these patients.

5. **Treatment with OTL-200 will delay cognitive decline in EJ patients**

OTL-200 has been shown to slow down the time for patients to experience a cognitive decline even in patients who had a decline in their motor function.

Justification: The results of the OTL-200 clinical trials show that no patient treated with OTL-200 had severe cognitive impairment (DQ<55). At a similar age, most of the natural history patients had a DQ score less than 55. 92% of OTL-200 patients retained normal cognitive ability (DQ>70) for the duration of the study follow-up period, whereas 85% of natural history patients had experienced severe cognitive impairment (DQ>55) (see Table D12: Developmental Quotient (Performance) Score for natural history patients during the OSR-TIGET natural history clinical trial follow-up period and Table D13).

Table D12: Developmental Quotient (Performance) Score for natural history patients during the OSR-TIGET natural history clinical trial follow-up period

Cognitive Ability	First reported DQp score		Last reported DQp score	
	LI	EJ	LI	EJ
Normal Cognitive Ability		[redacted]		[redacted]
Moderate Cognitive Impairment	[redacted]	[redacted]	[redacted]	[redacted]
Severe Cognitive Impairment		[redacted]		[redacted]

Table D13: Developmental Quotient (Performance) Score for OTL-200 treated patients during the OTL-200 clinical trial follow-up period

Cognitive Ability	First reported DQp score			Last reported DQp score		
	PS LI	PS EJ	ES EJ	PS LI	PS EJ	ES EJ
Normal Cognitive Ability (DQp ≥70)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Cognitive Impairment (70>DQp≥55)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Cognitive Impairment (DQp<55)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6. **Patients will progress through GMFC-MLD states sequentially and in ascending order (i.e. From GMFC-MLD 0 to GMFC-MLD 6)**

   The model uses GMFC-MLD states to track MLD disease progression through motor function. Modelled patients are assumed to pass through each of the GMFC-MLD health states sequentially (i.e. not skipping states) and in ascending order (i.e. moving from lower number (less severe) GMFC-MLD stages to higher number (more severe) GMFC-MLD stages.

   Justification: Based on clinical expert feedback, as the disease course is rapid, the progression of MLD can be documented through progressive GMFC-MLD stages. Monthly model cycle lengths were used to capture the rapid decline through each GMFC-MLD stage.

7. **Patients in the model will progress through each GMFC-MLD health state at time-independent exponential rates with one exception**

   The model transitions patients through each of the GMFC-MLD stages at exponential rates, not dependent on time, based on mean times to the next GMFC-MLD stage.

Justification: The use of constant (i.e. non-time dependent) rates of progression in the model was a simplifying model assumption approach adopted by the UK NICE independent analysis of the comparative clinical effectiveness and value of Ataluren and US ICER analysis of Deflazacort, Eteplirsen, and Golodirsen for Duchene Muscular Dystrophy (Landfeldt et al., 2017, Institute for Clinical and Economic Review, 2019), which is a similarly progressive neuromuscular disease, and was considered appropriate by key clinical experts. Given the number of states and the speed at which patients move within them, this method was selected over parametric survival curves to minimise the complexity in the model and ensure uncertainty can be captured using standard methods. However, transition probabilities for patients transitioning between GMFC-MLD 6 and death have been amended in this revised submission so that GMFC 6 survival is derived from parametric curves fitted to the LI and EJ natural history data to model survival beyond the trial period (see Appendix F for further information).

These assumptions were considered acceptable by key opinion leader (KOL) expert advisors, a leading modelling member of an ERG and a technology appraisal committee member consulted during model conceptualisation (Section 12.2.5). A full list of assumptions, justification and sources used in the model is provided in Table D14.

Table D14: Base case model assumptions

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
Treatment benefit				
1	OTL-200	OTL-200 will have a lifelong duration of effect in pre-symptomatic LI and EJ full responder patients because it is able to repopulate the brain with self-renewing gene corrected stem cells that are able to synthesise the missing ARSA enzyme, thereby preventing the onset of clinical manifestations of the disease. This is modelled as an expected lifetime delay to disease progression of 100 years.	KOL model conceptualisation (Orchard Data on file, 2020)	Use of sensitivity analyses that present differing time frames for “time to progression” to simulate differing durations of effect
2	OTL-200	OTL-200 will halt disease progression at GMFC-MLD 2 in LI and EJ partial-responder patients for a lifetime because some patients may experience a stabilisation of disease progression after some irreversible damage has occurred. Once the engraftment of gene-corrected cells and improvement in levels of the ARSA enzyme occurs prevention of further disease progression may take place. Engrafted cells in these patients are able to release ARSA enzymes at a sufficient rate and concentration to prevent further cell damage.	Clinical trial data and KOL model conceptualisation	Use of sensitivity analyses that present differing time frames for “duration of stabilisation”, “GMFC-MLD stage at stabilisation” and “proportion of patients stabilising” to simulate differing levels of MLD progression stabilisation
3	OTL-200	OTL-200 will slow down disease progression in LI and EJ partial-responder patients rather than halt progression because some irreversible damage may have occurred in patients, before the engraftment of gene-corrected cells and improvement in levels of the ARSA enzyme, leading to some degree of disease progression occurring. However, the progression would occur at a slower rate compared to untreated patients, who would still have deficient levels of the ARSA enzyme.	KOL model conceptualisation (Orchard Data on file, 2020)	Use of sensitivity analyses that present differing time frames for “progression modifier” to simulate differing levels of MLD progression protraction

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
4	OTL-200	OTL-200 requires some time for the effects to become apparent for EJ symptomatic patients given the time required for engraftment of the gene-corrected cells in the brain and synthesis of the ARSA enzyme. Pre-symptomatic LI and EJ patients will be treated prior to symptom onset so engraftment would occur prior to symptom onset.	Clinical expert feedback (Orchard Data on file, 2020)	Use of sensitivity analyses that present differing time frames for the “time to engraftment” to simulate optimistic and conservative scenarios
HCRU costs				
5	OTL-200 and BSC	The model currently utilizes HCRU values derived from a survey provided to 5 UK clinical experts in the form of a structured expert elicitation survey, however the model functionality allows users to modify health resource utilisation underlying MLD medical costs.	SEE (Orchard Data on file, 2020)	Use of sensitivity analyses
Cognitive Function				
6	OTL-200 and BSC	Cognitive sub-states are designated by Developmental Quotient performance (DQp) scores using the following categories to capture clinically meaningful cognitive decline in EJ patients: Normal or mild cognition: DQp ≥ 70 Moderately Impaired cognition: 70 > DQp ≥ 55 Severely impaired cognition: DQp < 55	Clinical expert feedback (Orchard Data on file, 2020)	-
7	OTL-200 and BSC	Cognitive function decline is not correlated with motor function decline in EJ patients and will be modeled separately using cognitive sub-states for each GMFC-MLD state. In LI patients, cognitive function declines at a similar rate with motor function and is captured in modelled LI health state utility scores. Once LI patients reach 48 months of age, they utilise PS EJ utility values and cognitive distributions to best align with the age of the underlying cohort used to develop the utility scores.	Clinical expert feedback (Orchard Data on file, 2020)	-

12.1.6 Define what the model's health states are intended to capture

The health states within the model capture the major motor function milestones observed in patients as well as associated complications and other features of MLD. Please see Table D15 for the health state descriptions.

Table D15: Functional status across health states

State	Motor features	Additional features
GMFC-MLD 0	Consistent with normal development for age	• Within a broad range of normal development *Normal Cognitive Function (DQp≥70):* o Brain functioning is similar to that of a developing child of the same age. *Moderate Cognitive Impairment (55<DQp<70):* o Brain functioning is worse than that of a developing child of the same age. o Sometime forget things and have trouble concentrating on tasks o Takes you longer to learn new skills o Communicate using simple sentences and gestures but longer to respond and form sentences *Severe Cognitive Impairment (DQp≤55):* o Brain functioning is much worse than that of a developing child of the same age. o Very limited in tasks that can be done and tasks require considerable effort o Minimal ability to learn new skills o Communicate occasionally with single words, smiling or crying. Can recognize pictures, shapes and family members

State	Motor features	Additional features
GMFC-MLD 1	Walking without support but with reduced quality of performance i.e. instability when standing or walking	• Unsteady when walking and some trouble with balance and running straight • No breathing difficulties • No problems swallowing or gripping food • No seizures • Bowel and bladder function is normal *Normal Cognitive Function (DQp≥70):* o Brain functioning is similar to that of a developing child of the same age. *Moderate Cognitive Impairment (55<DQp<70):* o Brain functioning is worse than that of a developing child of the same age. o Sometime forget things and have trouble concentrating on tasks o Takes you longer to learn new skills o Communicate using simple sentences and gestures but longer to respond and form sentences *Severe Cognitive Impairment (DQp≤55):* o Brain functioning is much worse than that of a developing child of the same age. o Very limited in tasks that can be done and tasks require considerable effort o Minimal ability to learn new skills o Communicate occasionally with single words, smiling or crying. Can recognize pictures, shapes and family members

State	Motor features	Additional features
GMFC-MLD 2	Walking without support not possible (fewer than five steps)	• A lot of difficulty with balance when walking. Walking without support is not possible. Cannot run or take part in any sports/exercise. • No breathing difficulties • No problems swallowing or but some issues gripping food • No seizures but some muscle stiffness • Bowel and bladder function is normal *Normal Cognitive Function (DQp≥70):* o Brain functioning is similar to that of a developing child of the same age. *Moderate Cognitive Impairment (55<DQp<70):* o Brain functioning is worse than that of a developing child of the same age. o Sometime forget things and have trouble concentrating on tasks o Takes you longer to learn new skills o Communicate using simple sentences and gestures but longer to respond and form sentences o Have disturbed sleep and feel irritated when it takes you longer to do the things you want to do *Severe Cognitive Impairment (DQp≤55):* o Brain functioning is much worse than that of a developing child of the same age. o Very limited in tasks that can be done and tasks require considerable effort o Minimal ability to learn new skills o Have disturbed sleep and feel very irritated when it takes you longer to do the things you want to do o Communicate occasionally with single words, smiling or crying. Can recognize pictures, shapes and family members

State	Motor features	Additional features
GMFC-MLD 3	Sitting without support and crawling/rolling is possible. Walking with support not possible	• Sitting with support but unable to walk with or without support. Need help washing and dressing. • No breathing difficulties • Some problems swallowing and gripping food and may be fed through a tube • Sometimes have seizures and have muscle stiffness and contractions with pain • Bowel and bladder function problems. Need to wear a pad/nappy. *Normal Cognitive Function (DQp≥70):* o Brain functioning is similar to that of a developing child of the same age. *Moderate Cognitive Impairment (55<DQp<70):* o Brain functioning is worse than that of a developing child of the same age. o Sometime forget things and have trouble concentrating on tasks o Takes you longer to learn new skills o Communicate using simple sentences and gestures but longer to respond and form sentences due to muscle stiffness. *Severe Cognitive Impairment (DQp≤55):* o Brain functioning is much worse than that of a developing child of the same age. o Very limited in tasks that can be done and tasks require considerable effort o Minimal ability to learn new skills o Communicate occasionally with single words, smiling or crying. Can recognize pictures, shapes and family members

State	Motor features	Additional features
GMFC-MLD 4	Sitting without support but no locomotion or sitting without support not possible, but locomotion such as crawling or rolling	• Unable to sitting without support or walk with or without support. Need help washing and dressing. • Sometimes have breathing difficulties • Unable to swallow and grip food and are fed through a tube and are losing weight • Frequent seizures and have severe muscle stiffness, frequent contractions, severe pain and your head and body lean to one side. • Have incontinence, need to wear a pad/nappy and have severe constipation and diarrhea *Normal Cognitive Function (DQp≥70):* o Brain functioning is similar to that of a developing child of the same age. o Due to severe muscle stiffness, it takes much longer to respond, form sentences and have people understand you. *Moderate Cognitive Impairment (55<DQp<70):* o Brain functioning is worse than that of a developing child of the same age. o Sometime forget things and have trouble concentrating on tasks o Takes you longer to learn new skills o Communicate using simple sentences and gestures but longer to respond and form sentences due to severe muscle stiffness *Severe Cognitive Impairment (DQp≤55):* o Brain functioning is much worse than that of a developing child of the same age. o Very limited in tasks that can be done and tasks require considerable effort o Minimal ability to learn new skills o Communicate occasionally with single words, smiling or crying but it takes you much longer to respond due to severe muscle stiffness. Can recognize pictures, shapes and family members

State	Motor features	Additional features
GMFC-MLD 5	No locomotion nor sitting without support, but head control is possible	• Some head control but unable to sitting without support or walk with or without support. Unable to wash or dress self. • Often have breathing difficulties • Unable to swallow and grip food and are fed through a tube and are losing weight • Very frequent seizures and have very severe muscle stiffness, frequent contractions, severe pain and your head and body lean to one side. • Have incontinence, need to wear a pad/nappy and have severe constipation and diarrhea *Normal Cognitive Function (DQp≥70):* o Brain functioning is similar to that of a developing child of the same age. o Due to severe muscle stiffness, it takes much longer to respond, form sentences and have people understand you. *Moderate Cognitive Impairment (55<DQp<70):* o Brain functioning is worse than that of a developing child of the same age. o Sometime forget things and have trouble concentrating on tasks o Takes you longer to learn new skills o Communicate using simple sentences and gestures but takes much longer and more effort to respond and form sentences due to very severe muscle stiffness *Severe Cognitive Impairment (DQp≤55):* o Brain functioning is much worse than that of a developing child of the same age. o Very limited in tasks that can be done and tasks require considerable effort o Minimal ability to learn new skills o Communicate with some groans, smiling or crying but it takes much longer and more effort to respond due to very severe muscle stiffness. Can recognize pictures, shapes and family members

State	Motor features	Additional features
GMFC-MLD 6	Loss of any locomotion as well as loss of any head and trunk control	• Unable to move. Unable to wash or dress self. • Have breathing difficulties all the time • Unable to swallow and grip food and are fed through a tube and are losing weight • Little feeling in muscles and very frequent muscle contraction with severe pain. Very frequent seizures with medication for them. • Have incontinence, need to wear a pad/nappy and have severe constipation and diarrhea *Normal Cognitive Function (DQp≥70):* o Brain functioning is similar to that of a developing child of the same age. o Due to severe muscle stiffness, it takes much longer to respond, form sentences and have people understand you. *Moderate Cognitive Impairment (55<DQp<70):* o Brain functioning is worse than that of a developing child of the same age. o Sometime forget things and have trouble concentrating on tasks o Takes you longer to learn new skills o Communicate using simple sentences and gestures but longer to respond and form sentences *Severe Cognitive Impairment (DQp≤55):* o Brain functioning is much worse than that of a developing child of the same age. o Very limited in tasks that can be done and tasks require considerable effort o No ability to learn new skills o Communicate only with some simple facial expressions, movements, smiling or crying and it takes much longer and more effort to respond due to very severe muscle stiffness. Can recognize pictures, shapes and some family members

Abbreviations: DQp, Developmental Quotient performance scale. GMFC-MLD, Gross Motor Function Classification-MLD.
Note: Cognitive sub-states only relevant for EJ patients.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in Table D16.

Table D16: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime horizon.	NICE guidance states that model time horizons should be long enough to capture all benefits of the treatment. In MLD, gene therapy has the potential of extending life so benefits and costs should be followed for a lifetime time horizon.	NICE guide to the methods of technology appraisal 2013 Interim Process and Methods of the HST (16, 17)
Discount for costs and outcomes	1.5% and 3.5% for scenario analysis	1.5% was used in line with NICE HST guidance and on basis of the evidence that long-term health benefits are likely to be achieved	NICE guide to the methods of technology appraisal 2013 Interim Process and Methods of the HST (16, 17)
Perspective (NHS/PSS)	NHS in England	In line with NICE guidance.	NICE guide to the methods of technology appraisal 2013 Interim Process and Methods of the HST (16, 17)
Cycle length	1-month cycles for duration of model	A monthly model cycle was selected to allow changes in childhood development and milestone achievement to be adequately captured.	KOL verified – model conceptualisation

Abbreviations: KOL, key opinion leader; NHS, National Health Service; MLD, metachromatic leukodystrophy

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

12.2.1.1 Gross Motor Function

Best supportive care (BSC)

For the base case, patients in the BSC LI and EJ arms are assumed to experience MLD disease progression through GMFC-MLD stages at rates derived from the age and disease subtype matched natural history cohorts used as the comparator cohort for the OTL-200 clinical trial (i.e. OSR-TIGET natural history study). As it was not practically possible to identify and manage MLD patients with BSC pre-symptomatically, patients entered the OSR-TIGET natural history study in GMFC-MLD stage 1 or higher. To align with the pre-symptomatic OTL-200 treated Late Infantile and Early Juvenile populations in the model, the average time from GMFC-MLD 0 to GMFC-MLD 1 was derived from the initiation of follow-up at 10 months observed in the Elgun 2019 study's Late Infantile population for Late Infantile patients in the model. The average age of symptom onset for Early Juvenile patients (between 30 months and 7 years) was based on key clinical opinion leader feedback.

To allow users to configure model parameters and underlying data, alternative rates of MLD progression for the LI and EJ populations were included based on observed data from the following natural history sources:

- Elgun, 2019 (Elgun et al., 2019)
- Kehrer, 2011 (Kehrer et al., 2011a)

The Elgun, 2019 and Kehrer, 2011 data were digitised from the published figures (provided in Supplementary Excel document), however, instead of reporting the time to transition from GMFC-MLD 2 to GMFC-MLD 3, GMFCMLD 3 to GMFC-MLD 4 and GMFC-MLD 4 to GMFC-MLD 5, only the time to transition from GMFC-MLD 2 to GMFC-MLD 5 was reported. Since the economic model requires inputs for the time to each GMFC-MLD stage, the mean time from GMFC-MLD 2 to GMFC-MLD 5 was calculated and that value was distributed between the intermediate stages (i.e. GMFC-MLD 2 to GMFC-MLD 3, GMFC-MLD 3 to GMFC-MLD 4 and GMFC-MLD 4 to GMFC-MLD 5) using the distribution of time spent in each GMFC-MLD stage from the OSR-TIGET Natural history study.

OTL-200

For the base case, motor function data have been derived from a post-hoc analysis of the indicated population (IP, n = [redacted]) within the Integrated Data Set (IDS; n=29) of patients treated in the registrational study (201222), and 3 EAPs (Compassionate use (CUP) (206258), Hospital exemption (205029) and Compassionate use (CO2) (207394)). Data from [redacted] patients in the integrated dataset were excluded from this post hoc analysis, as these patients would not be eligible for OTL-200 as per the approved EMA indication. More specifically, [redacted] were ES EJ patients who were treated after they entered rapid disease progression and [redacted] was a LI patient symptomatic at treatment.

Data from the indicated population was analysed by aggregating each eligible patient's data and tracking their GMFC-MLD stage over time to determine the amount of time required to transition from one GMFC-MLD stage to another for each patient from each trial. This resulted in a total patient number used for the data to [redacted] patients overall with [redacted] LI patients and [redacted] EJ patients (Pivotal (201222), LI Cohort: [redacted] patients, EJ Cohort: [redacted] patients; CUP (206258), LI Cohort: [redacted] patients, EJ Cohort: [redacted] patient; Hospital exemption (205029), LI Cohort: [redacted] patients; CO2 (207394), EJ Cohort: [redacted]) (Refer to Section 9 for more details).

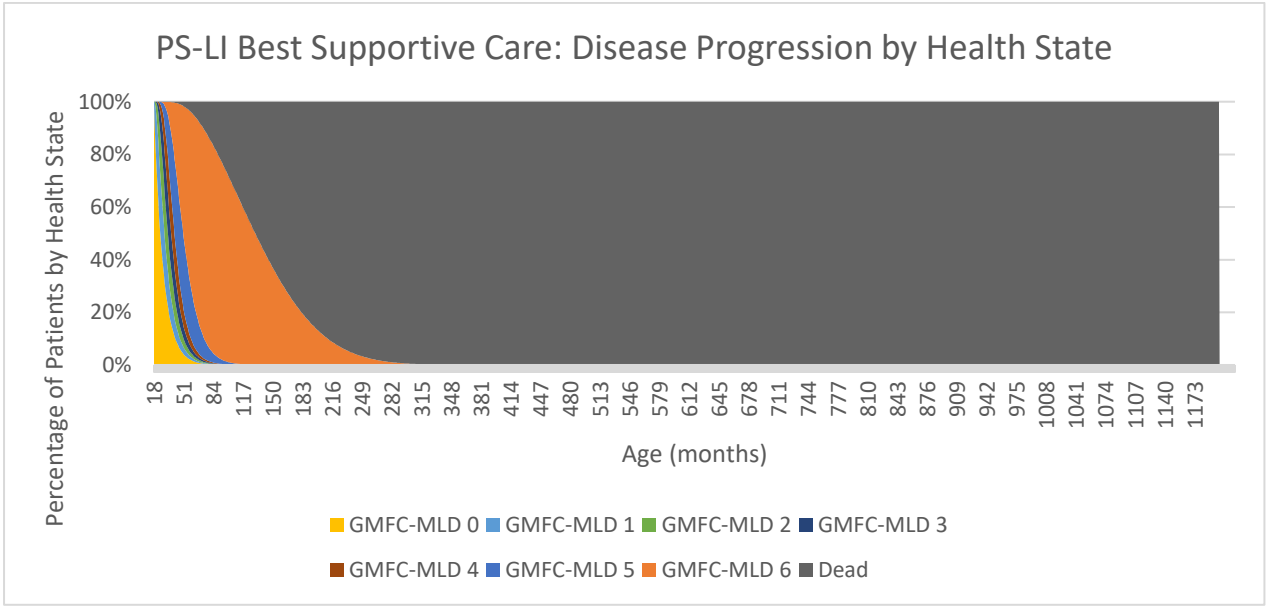
A technical consideration when pooling the data from the clinical trials for the revised economic model is the difference in follow-up periods of each respective trial. The pre-specified primary time point for analysis in the clinical trials was 2 years post treatment/baseline, but patients are continuing to be followed beyond 2 years. All patients in the pivotal study (201222), Hospital exemption (205029) and CO2 (207394) reached the 2-year follow-up endpoint. None of the patients in CUP (206258) reached the 2-year follow-up endpoint, but all eligible patients are continuing follow-up.

Patients were categorised into three cohorts that were modelled separately: PS LI, PS EJ and ES EJ based on the eligible patient population's symptomatic status at the point of treatment in the Orchard Therapeutics clinical trials. Within each of these cohorts, OTL-200 treated patients were

categorised as either full-responders or partial responders. Given that ES EJ patients were, by definition, symptomatic at treatment, they were all considered to be partial-responders. A responder classification of each OTL-200 treated patient in the indicated population is presented in Appendix D.

Figure D4, Figure D5, and Figure D6 show the health state progression over the course of a lifetime for BSC and OTL-200 treated patients, utilising the base case model parameters for each disease variant. The differences in the two figures highlight the larger proportions of treated patients in GMFC-MLD 0 showing the effect of halting the disease progression.

Figure D4: PS LI population cohort by health state and age (BSC vs. OTL-200)



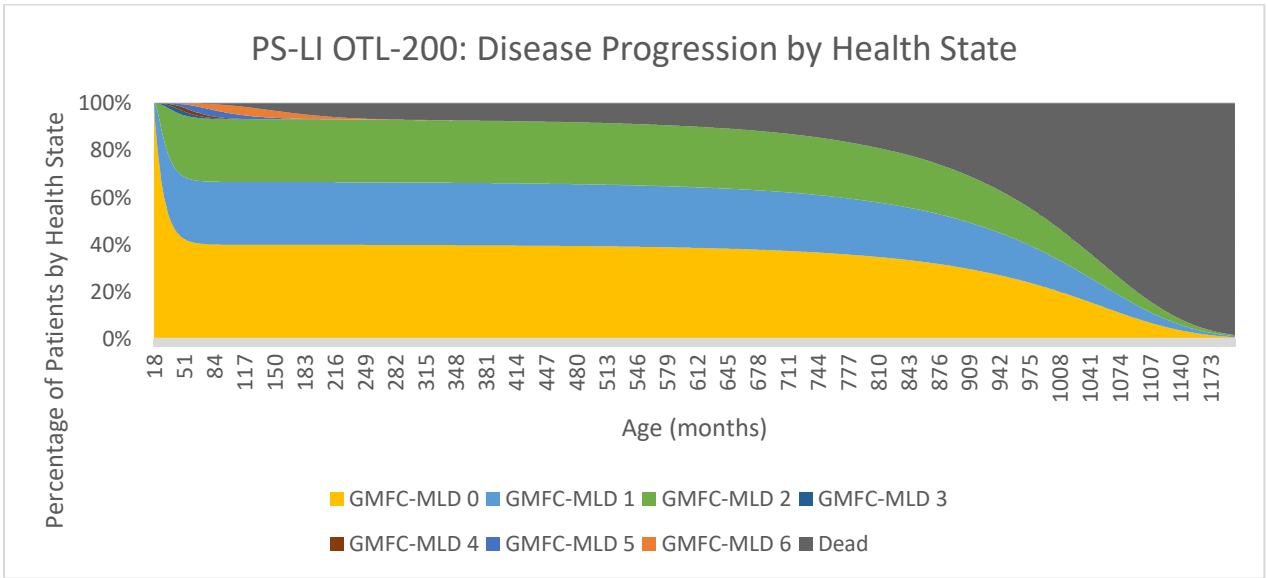
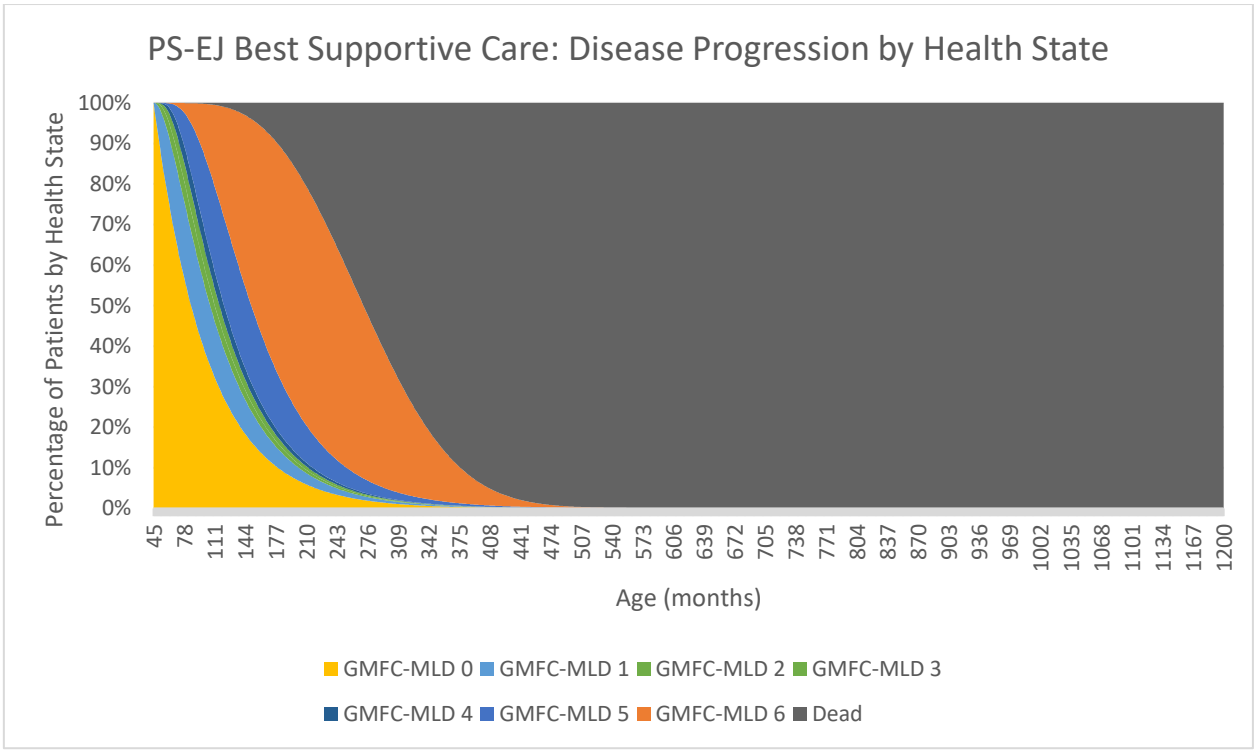


Figure D5: PS EJ population cohort by health state and age (BSC vs. OTL-200)



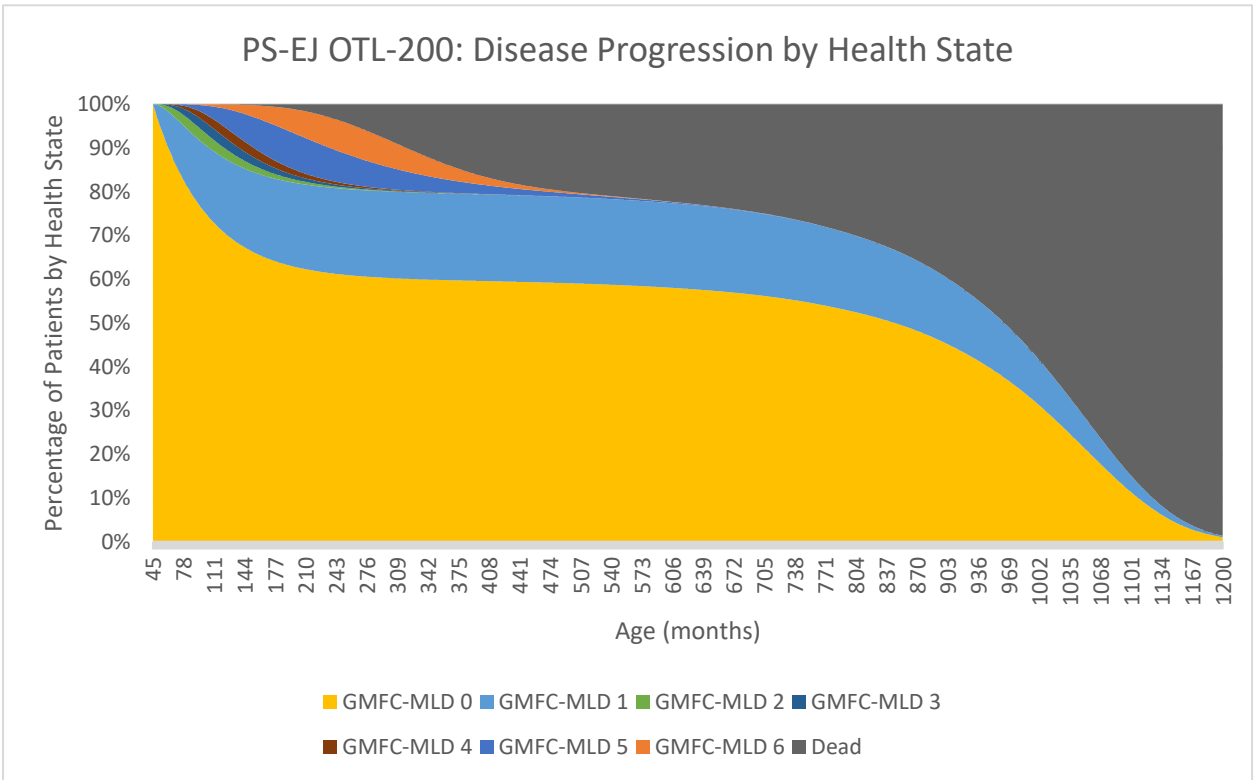
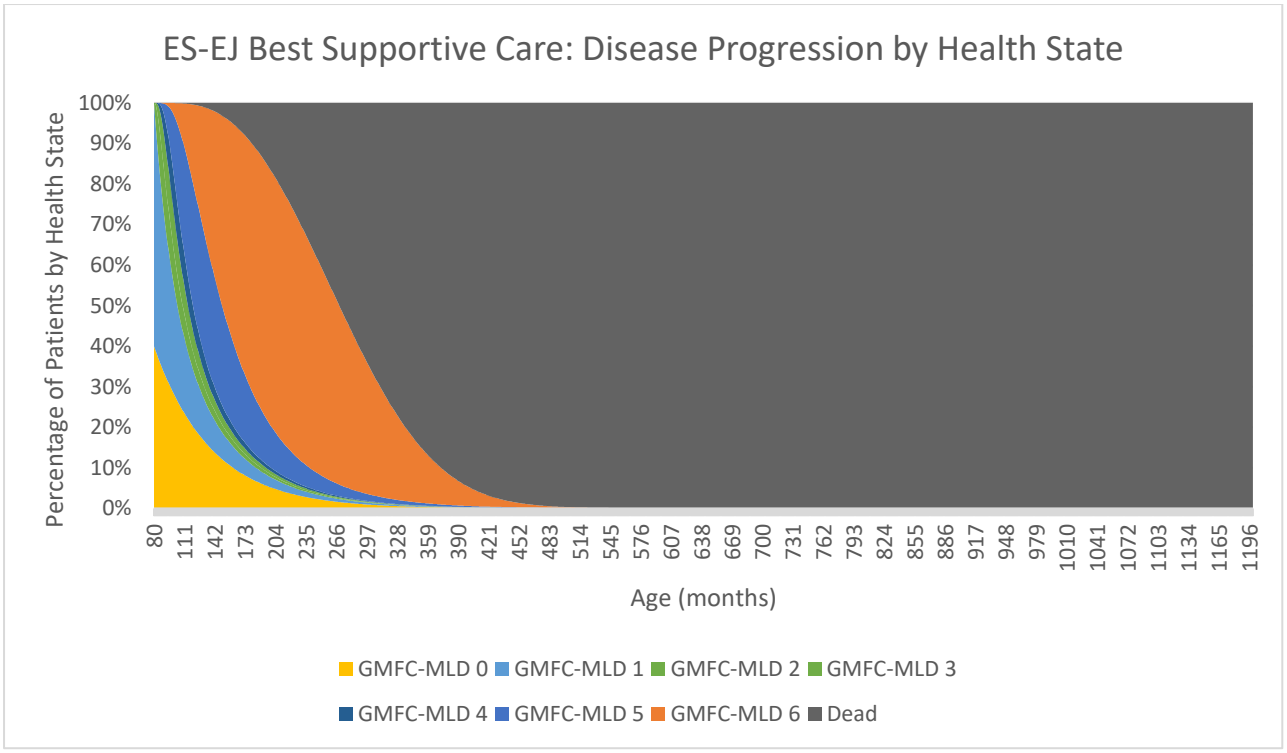
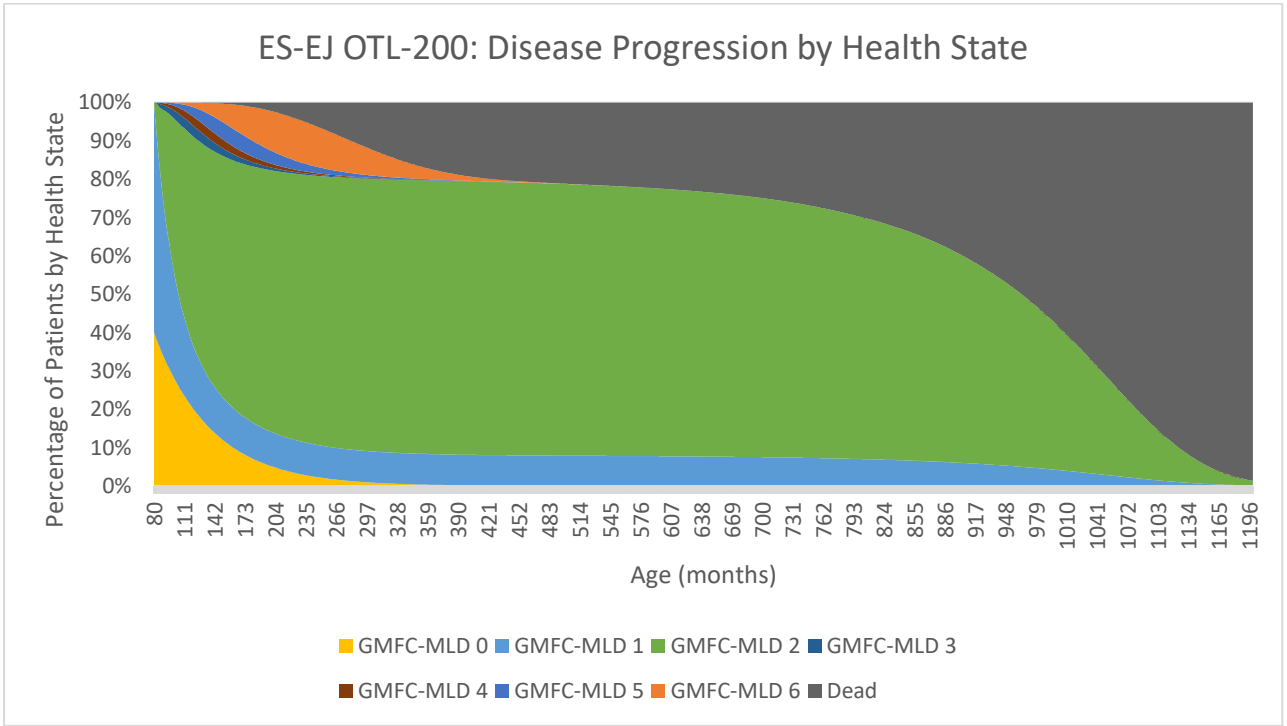


Figure D6: ES EJ population cohort by health state and age (BSC vs. OTL-200)





12.2.1.2 Cognitive function

Patient distributions into the cognitive sub-states were developed for each of the EJ cohorts based on DQp data collected in the OTL-200 clinical trials and

clinical expert feedback (cognitive sub-state distributions are provided in Appendix D). At each cycle for each GMFC-MLD state, patients were allocated into cognitive sub-states based on these distributions (See Table D17, Table D18 and Table D19 below for example).

Table D17: PS EJ BSC cognitive sub-state distribution by GMFC-MLD stage

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for “After Cognitive Decline: GMFC-MLD 0”, “GMFC-MLD 1”, “GMFC-MLD 2”, and “GMFC-MLD 6” provided by results of SEE (11). Values for GMFC-MLD 3, 4 and 5 derived from an assumed linear decline between known values. Values for “Before Cognitive Decline: GMFC-MLD 0” assumed based on prior clinical expert input.
*Time until cognitive decline derived from difference between 57 mo. (average EJ onset

occurring between 30 months and 7 years) and 45 months (age at PS EJ model entry.

Table D18: PS EJ OTL-200 full-responder cognitive sub-state distribution by GMFC-MLD stage

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for GMFC-MLD 5 and GMFC-MLD 6 assumed to utilize BSC values. All other cognitive distribution values informed by clinical trial DQp data and clinical expert opinion.
*Time until cognitive decline derived from difference between 16 years (max. follow-up time in Orchard Therapeutics clinical trial) and 45 months (age at PS EJ model entry) based on

clinical expert advice

Table D19: PS EJ OTL-200 partial-responder cognitive sub-state distribution by GMFC-MLD stage

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for GMFC-MLD 5 and GMFC-MLD 6 assumed to utilize BSC values. All other cognitive distribution values informed by clinical trial DQp data and clinical expert opinion.
*Time until cognitive decline derived from difference between 16 years (max. follow-up time in Orchard Therapeutics clinical trial) and 45 months (age at PS EJ model entry) based on clinical expert advice.

12.2.1.3 Survival

Survival in each health state was informed by observed clinical trial data and, while patients were required to transition to GMFC-MLD 6 to experience death due to MLD-related mortality, patients were able to transition to death from all GMFC-MLD states. Patients in GMFC-MLD 0-5 used the UK general population all-cause mortality rate (20) to transition to death. Patients in GMFC-MLD 6 transitioned to death based upon parametric curves fitted to the LI and EJ natural history data (see Appendix F for full information) while also including all-cause mortality, given the assumption informed by the OSR-TIGET natural history data that MLD patients would have progress to GMFC-MLD 6 prior to progressing to disease related death.

The mean age at death for the PS LI, PS EJ and ES EJ BSC model arms, calculated by summing the BSC mean time to transition values presented in associated Table D8, Table D9, or Table D10, was validated by clinical experts in the SEE and against published mean age at death values (see Table D20 below for comparison).

Table D20: Comparison of mean age at death in the model and published literature by disease variant

Disease Variant	Modelled Mean Age at Death (BSC)	Published Mean Age at Death
PS LI	[redacted]	4.2 years
PS EJ	[redacted]	17.4 years*
ES EJ	[redacted]	17.4 years*

*Mean age at death estimated from all juvenile (early and late juvenile) MLD patients
Source: (Mahmood et al., 2010)

Differences between the published mean age at death for the PS LI population and modelled mean age at death is likely due to the length of time OSR-TIGET natural history patients spent in GMFC-MLD 6 prior to death (i.e. 57 months), which may reflect improved MLD management in the natural history trial setting in the last few years. Based on the estimates in Table D8, PS LI patients enter GMFC-MLD 6 at 4.2 years of age, which closely aligns with the published mean age at death. However, the modelled mean age at death could be reflective of improved MLD management practices.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

MLD-related care costs are extrapolated beyond the study follow-up period. A *de novo* study estimated UK healthcare resource use (HCRU) costs associated with the management of MLD, based on aggregated data from n=5 clinical experts (October 2020). Details of the recruitment and inclusion criteria used to select the clinical experts are provided in the SEE study report. (Orchard Data on file, 2020) These costs are applied for the duration that

individuals remain in each health state for the time horizon of the model (life time).

Clinical outcomes were also extrapolated beyond the study follow-up period, with the expected clinical benefit captured through the assumptions and clinical parameters described in Section 12.1.5 above.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The cost-effectiveness model does not use any intermediate outcome measures, rather only final clinical outcome measures (i.e. disease progression and time to death).

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

No adverse events were included the in cost-effectiveness analysis. While it is recognised that the safety findings following treatment with OTL-200 are consistent with what would be expected in patients with MLD and who have undergone busulfan conditioning and subsequent haematological reconstitution, these adverse events are known to be temporal and self-limiting. In addition, the concentration of busulfan required for OTL-200 conditioning is lower than that of conventional HSC transplants, which tend to also involve multiple other chemotherapeutic agents. No treatment related serious adverse events were observed in the clinical trials. In addition most of the adverse events in the clinical trials were temporal and resolved spontaneously. As such, adverse events are not expected to have a significant impact on HRQoL or resource use.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The suitability of each clinical model parameter and input was determined through a two-step process:

i. Exploratory discussion of proposed model structure and clinical inputs with three leading globally renowned MLD specialists:

   a. [redacted]

   b. [redacted]

   c. [redacted]

   *Also has direct experience of treating MLD patients with OTL-200

ii. A formal Structured Expert Elicitation process with 6 UK MLD specialists:

   a. [redacted]

   b. [redacted]

   c. [redacted]

   d. [redacted]

   e. [redacted]

f. [redacted]

A de novo study estimated the clinical impact of MLD disease progression and OTL-200 treatment in MLD patients, based on aggregated data from n=6 clinical experts (October 2020). Details of the recruitment and inclusion criteria used to select the clinical experts are provided in the SEE study report. (Orchard Data on file, 2020)

Clinical experts

Six clinical experts were identified from all three lysosomal storage disorders reference centres in the UK, in which metachromatic leukodystrophy (MLD) patients are managed: St Mary's Children Hospital, Manchester; Great Ormond Street Hospital, London; and Birmingham Children's Hospital. Clinical experts were identified based on their expertise in MLD, or related disorders, and prior experience of treating MLD in UK clinical practice. Although none of the experts had direct experience of administering OTL-200 to patients, some were responsible for managing patients who had received treatment with OTL-200 as part of the clinical trials in Milan, Italy. Individuals were selected to best represent the range of healthcare professionals known to treat MLD and included paediatric haematologists, consultants in paediatric inherited metabolic diseases, and clinical neuropsychologists. Collectively, these experts were considered to provide good representation of the clinical expertise in MLD across the UK. The n=6 clinical experts included: Five consultant paediatric inherited metabolic diseases and one clinical neuropsychologist. Clinical experts were based in the Greater Manchester (n=1), Birmingham (n=1) and Greater London (n=4).

Methods

Each clinical expert took part in an individual, web-based survey, which quantified specific clinical input values using a structured and systematic survey. Clinical experts were asked to provide information on the progression modifier values and cognitive sub-state distributions for OTL-200 treated patients in each disease cohort at varying GMFC-MLD stages. Weighted means for each response provided were calculated and informed a second

individual, web-based survey, provided to clinical experts. When the results of the first questionnaire were reported, the individual anonymised responses were presented alongside the aggregate data. Additional questions regarding stabilised patients (i.e. GMFC-MLD stage at stabilisation, proportion of patients likely to stabilise) were posed to experts based on responses in the prior survey. Aggregated mean results from the second round were considered for inclusion as values for parameters in the health economic model.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in Table D21 below.

Table D21: Summary of variables applied in the cost-effectiveness model

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Discounting				
Discount rate (costs)	1.5%	N/A for PSA	NICE guide to the methods of technology appraisal 2013, NICE Process and Methods of the HST (National Institute for Health and Care Excellence, 2013, National Institute for Health and Care Excellence, 2017)	12.1.7
Discount rate (outcomes)	1.5%	N/A for PSA		
Combined MLD Population Weightings				
Proportion PS LI	[redacted]	SE: 20% (Dirichlet)	Derived from convergence of epidemiologic sources and clinical expert responses provided in structured expert elicitation (Orchard Data on file, 2020)	12.1.3
Proportion PS EJ	[redacted]			
Proportion ES EJ	[redacted]			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Costs				
Monthly MLD care costs				
GMFC-MLD 0 total (Age 0 – 5)	£49	SE: £10 (Gamma)	Average monthly cost of one annual inpatient hospitalisation for GMFC 0 patients < 18 – No MLD disease progression in GMFC-MLD 0.	12.3.1
GMFC-MLD 1 total (Age 0 – 5)	£1,062	SE: £212 (Gamma)	Itemised total from healthcare resource utilisation structured expert elicitation (Aggregate of Drugs, Medical Tests, Medical Visits, Hospitalisations, GP & Emergency, Health Materials and Social Services) (Orchard Data on file, 2020)	
GMFC-MLD 2 total (Age 0 – 5)	£1,307	SE: £261 (Gamma)		
GMFC-MLD 3 total (Age 0 – 5)	£1,784	SE: £357 (Gamma)		
GMFC-MLD 4 total (Age 0 – 5)	£11,759	SE: £2,352 (Gamma)		
GMFC-MLD 5 total (Age 0 – 5)	£11,880	SE: £2,376 (Gamma)		
GMFC-MLD 6 (At Home) total (Age 0 – 5)	£17,104	SE: £3,421 (Gamma)		
GMFC-MLD 6 (In Hospital) total (Age 0 – 5)	£23,319	SE: £4,664 (Gamma)		
GMFC-MLD 0 total (Age 6 – 18)	£49	SE: £10 (Gamma)	Average monthly cost of one annual inpatient hospitalisation for GMFC 0 patients < 18 – No MLD disease progression in GMFC-MLD 0.	
GMFC-MLD 1 total (Age 6 – 18)	£1,062	SE: £212 (Gamma)		
GMFC-MLD 2 total (Age 6 – 18)	£1,307	SE: £261 (Gamma)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 3 total (Age 6 – 18)	£1,784	SE: £357 (Gamma)	Itemised total from healthcare resource utilisation structured expert elicitation (Aggregate of Drugs, Medical Tests, Medical Visits, Hospitalisations, GP & Emergency, Health Materials and Social Services) (Orchard Data on file, 2020)	
GMFC-MLD 4 total (Age 6 – 18)	£11,759	SE: £2,352 (Gamma)		
GMFC-MLD 5 total (Age 6 – 18)	£11,880	SE: £2,376 (Gamma)		
GMFC-MLD 6 (At Home) total (Age 6 – 18)	£17,104	SE: £3,421 (Gamma)		
GMFC-MLD 6 (In Hospital) total (Age 6 – 18)	£23,319	SE: £4,664 (Gamma)		
GMFC-MLD 0 total (Age 19+)	£0	SE: £0 (Gamma)	No MLD associated direct medical costs – No MLD disease progression in GMFC-MLD 0.	
GMFC-MLD 1 total (Age 19+)	£1,062	SE: £212 (Gamma)	Itemised total from healthcare resource utilisation structured expert elicitation (Aggregate of Drugs, Medical Tests, Medical Visits, Hospitalisations, GP & Emergency, Health Materials and Social Services) (Orchard Data on file, 2020)	
GMFC-MLD 2 total (Age 19+)	£1,307	SE: £261 (Gamma)		
GMFC-MLD 3 total (Age 19+)	£1,784	SE: £357 (Gamma)		
GMFC-MLD 4 total (Age 19+)	£11,954	SE: £2,391 (Gamma)		
GMFC-MLD 5 total (Age 19+)	£12,077	SE: £2,415 (Gamma)		
GMFC-MLD 6 (At Home) total (Age 19+)	£17,398	SE: £3,480 (Gamma)		
GMFC-MLD 6 (In Hospital) total (Age 19+)	£23,502	SE: £4,700 (Gamma)		
Percentage of GMFC-MLD 6 patients living at home (vs. in hospital)	80%	SE: 0.16 (Beta)	Clinical expert advice	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
OTL-200 costs				
OTL-200 drug acquisition cost	[redacted]	Fixed in PSA SE: 20% [redacted] in DSA *SE: 20% [redacted] in DSA	Ex-factory (List) Price *Patient Access Scheme (PAS) Price ([redacted] % discount)	**Error! Reference source not found.**
OTL-200 administration: Leukapheresis (cell harvest)	£4,272	SE: £854 (Gamma)	Weighted average of HRGs for stem cell (SA34Z) and bone marrow harvest (SA18Z). National Reference costs – 2018/19	12.3.6
OTL-200 administration: Conditioning	£7,899	SE: £1,580 (Gamma)	Hospitalisation for conditioning ([redacted] days) based on clinical expert opinion (Prof Rob Wynn) and SmPC. HRG for paediatric metabolic disorders hospitalisation non-elective inpatients (weighted average cost = £7,761) Busulfan costs = £138 per patient (eMIT 2019 database Busulfan 60mg vial – 8 pack = £367.81), average dose of Busulfan in clinical trials = 176.102mg	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
OTL-200 administration: Administration and hospitalisation	£24,188	SE: £4,838 (Gamma)	HRG paediatric metabolic disorders admissions weighted average elective inpatient (weighted average cost = £5,068). However, the SMPC states patient would stay between [redacted] weeks (average of [redacted] weeks) in the hospital, which is about [redacted] weeks longer than that reported for metabolic disorders inpatient admissions in Hospital Episode Statistic of 11 days (E75.2). The weighted average cost of elective inpatient excess bed day HRGs was calculated to be £460.73 (i.e. £5,068 /11). Thus, overall hospital stay equivalent to be £24,188 (i.e. £5068 + [41.5 x 460.73])	
OTL-200 administration: Follow-up transplant costs	£61,965	SE: £12,393 (Gamma)	Hettle et al (22) – NICE Regenerative Medicines Report. 2017. Follow-up costs for allogeneic stem cell transplants. Discharge to 6 months = £28,390, 6–12 months = £19,502, 12–24 months = £14,073. Expert opinion is follow-up for autologous transplants costs will be the same as for allogeneic stem cell transplants, and patients will be discharged to metabolic care after 2 years. Follow-up transplant costs evenly distributed over the first 2 years of model	
Quality of life adjustments				

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Utility: GMFC-MLD 0 (EJ Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)	Orchard Therapeutics Utility Study TTO Values (Nafees et al., 2020 Unpublished)	7.1
Utility: GMFC-MLD 0 (EJ Severe Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 1 (LI)	[redacted]	SE: 0.034 (Normal)		
Utility: GMFC-MLD 1 (EJ Normal Cognition)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 1 (EJ Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 1 (EJ Severe Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 2 (LI)	[redacted]	SE: 0.042 (Normal)		
Utility: GMFC-MLD 2 (EJ Normal Cognition)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 2 (EJ Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 2 (EJ Severe Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 3 (LI)	[redacted]	SE: 0.065 (Normal)		
Utility: GMFC-MLD 3 (EJ Normal Cognition)	[redacted]	SE: 0.005 (Normal)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Utility: GMFC-MLD 3 (EJ Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 3 (EJ Severe Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 4 (LI)	[redacted]	SE: 0.059 (Normal)		
Utility: GMFC-MLD 4 (EJ Normal Cognition)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 4 (EJ Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 4 (EJ Severe Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 5 (LI)	[redacted]	SE: 0.059 (Normal)		
Utility: GMFC-MLD 5 (EJ Normal Cognition)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 5 (EJ Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 5 (EJ Severe Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 6 (LI)	[redacted]	SE: 0.055 (Normal)		
Utility: GMFC-MLD 6 (EJ Normal Cognition)	[redacted]	SE: 0.005 (Normal)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Utility: GMFC-MLD 6 (EJ Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility: GMFC-MLD 6 (EJ Severe Cognitive Impairment)	[redacted]	SE: 0.005 (Normal)		
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): % male in equation	[redacted]	SE: 0.0247 (Beta)	Ara and Brazier 2010 (Ara and Brazier, 2010)	**Error! Reference source not found.**
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation intercept	[redacted]	SE: 0.0475 (Normal)		
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation sex coefficient	[redacted]	SE: 0.0011 (Normal)		
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation age coefficient	[redacted]	SE: 0.000013 (Normal)		
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation age^2 coefficient	[redacted]	SE: 0.000002 (Normal)		
Disutility: Caregiver Disutility	[redacted]	SE: 0.004 (Normal)	UK Caregiver Utility Score Survey (Pixuvri SmPC, 2019, Pang et al., 2020)	7.1
Caregiver Disutility: Number of Caregiver (GMFC-MLD 0)	0	SE: 0.000 (Normal)	Clinical Assumption	
Caregiver Disutility: Number of Caregiver (GMFC-MLD 1)	0	SE: 0.000 (Normal)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Caregiver Disutility: Number of Caregiver (GMFC-MLD 2)	0	SE: 0.000 (Normal)		
Caregiver Disutility: Number of Caregiver (GMFC-MLD 3)	0	SE: 0.000 (Normal)		
Caregiver Disutility: Number of Caregiver (GMFC-MLD 4)	0	SE: 0.040 (Normal)		
Caregiver Disutility: Number of Caregiver (GMFC-MLD 5)	2	SE: 0.040 (Normal)		
Caregiver Disutility: Number of Caregiver (GMFC-MLD 6)	2	SE: 0.040 (Normal)		
EJ Cognitive Substate Distributions				
Time until cognitive decline (months) (BSC)	12	SE: 0.240 (Normal)	Clinical Expert Opinion based upon the mean age of MLD symptom onset and the age at entry into the model	
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (BSC)	[redacted]	SE: 20% (Dirichlet)	Clinical expert opinion based on Orchard Therapeutics OTL-200 clinical trial DQ (performance) data	12.2.1
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (BSC)	[redacted]			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (BSC)	[redacted]	SE: 49% (Dirichlet)	Distribution values derived from clinical expert responses provided in structured expert elicitation (Orchard Data on file, 2020)	
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 1: Normal Cognition (BSC)	[redacted]	SE: 22%, 20%, 34% (Dirichlet)		
GMFC-MLD 1: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 1: Severe Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 2: Normal Cognition (BSC)	[redacted]	SE: 36%, 20%, 41% (Dirichlet)		
GMFC-MLD 2: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 2: Severe Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 3: Normal Cognition (BSC)	[redacted]	SE: 20% (Dirichlet)	Distribution values derived from assumed linear decline between clinical expert responses provided in structured expert elicitation in GMFC-MLD 2 and GMFC-MLD 6 (Orchard Data on file, 2020)	
GMFC-MLD 3: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 3: Severe Cognitive Impairment (BSC)	[redacted]			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 4: Normal Cognition (BSC)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 4: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 4: Severe Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 5: Normal Cognition (BSC)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 5: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 5: Severe Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 6: Normal Cognition (BSC)	[redacted]	SE: 60%, 20%, 9% (Dirichlet)	Distribution values derived from clinical expert responses provided in structured expert elicitation (Orchard Data on file, 2020)	
GMFC-MLD 6: Cognitive Impairment (BSC)	[redacted]			
GMFC-MLD 6: Severe Cognitive Impairment (BSC)	[redacted]			
Time until cognitive decline (months) (OTL-200 Pre-symptomatic Full Responder)	[redacted]	SE: 2.940 (Normal)	Clinical expert opinion based on the maximum follow-up time from the OTL-200 Clinical Trial	
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	SE: 20% (Dirichlet)	Clinical expert opinion based on OTL-200 Clinical Trial DQ (performance) data	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 1: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 1: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 2: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 2: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 3: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 3: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 4: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 4: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 5: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	[redacted]	SE: 20% (Dirichlet)	Distribution values assumed to be equal to BSC values for GMFC-MLD 5 and 6. (Orchard Data on file, 2020)	
GMFC-MLD 5: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]			
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]			
GMFC-MLD 6: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	[redacted]	SE: 60%, 20%, 9% (Dirichlet)		
GMFC-MLD 6: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]			
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]			
Time until cognitive decline (months) (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 2.940 (Normal)	Clinical expert opinion based on the maximum follow-up time from the OTL-200 Clinical Trial	
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)	Clinical expert opinion based on OTL-200 Clinical Trial DQ (performance) data	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 1: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 1: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 2: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 2: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 3: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 3: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 4: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 4: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 5: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)	Distribution values assumed to be equal to BSC values for GMFC-MLD 5 and 6. (Orchard Data on file, 2020)	
GMFC-MLD 5: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 6: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	SE: 60%, 20%, 9% (Dirichlet)		
GMFC-MLD 6: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]			
Time until cognitive decline (months) (OTL-200 Symptomatic Full Responder)	112	SE: 2.240 (Normal)	Clinical expert opinion based on the maximum follow-up time from the OTL-200 Clinical Trial	
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	SE: 20% (Dirichlet)	Clinical expert opinion based on OTL-200 Clinical Trial DQ (performance) data	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 1: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 1: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 2: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 2: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 3: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 3: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 4: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	SE: 20% (Dirichlet)		
GMFC-MLD 4: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 5: Normal Cognition (OTL-200 Symptomatic Full Responder)	[redacted]	SE: 20% (Dirichlet)	Distribution values assumed to be equal to BSC values for GMFC-MLD 5 and 6. (Orchard Data on file, 2020)	
GMFC-MLD 5: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	[redacted]			
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	[redacted]			
GMFC-MLD 6: Normal Cognition (OTL-200 Symptomatic Full Responder)	[redacted]	SE: 60%, 20%, 9% (Dirichlet)		
GMFC-MLD 6: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	[redacted]			
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	[redacted]			
Time until cognitive decline (months) (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 2.240 (Normal)	Clinical expert opinion based on the maximum follow-up time from the OTL-200 Clinical Trial	
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)	Clinical expert opinion based on OTL-200 Clinical Trial DQ (performance) data	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 1: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 1: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 2: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 2: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 3: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 3: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 4: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)		
GMFC-MLD 4: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
GMFC-MLD 5: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 20% (Dirichlet)	Distribution values assumed to be equal to BSC values for GMFC-MLD 5 and 6. (Orchard Data on file, 2020)	
GMFC-MLD 5: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 6: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	SE: 60%, 20%, 9% (Dirichlet)		
GMFC-MLD 6: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]			
Clinical Inputs				
Mean time to transition GMFC-MLD 0 to 1: LI BSC	10.33	SE: 0.207 (Normal)	Time until entry into GMFC-MLD 1 (Elgun, 2019) (18)	12.2.1
Mean time to transition GMFC-MLD 1 to 2: LI BSC	[redacted]	SE: 0.919 (Normal)	OSR-TIGET natural history data	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Mean time to transition GMFC-MLD 2 to 3: LI BSC	[redacted]	SE: 0.629 (Normal)	OSR-TIGET natural history data for GMFC-MLD 2 to GMFC-MLD 5 split evenly between GMFC-MLD 2 to 3, GMFC-MLD 3 to 4 and GMFC-MLD 4 to 5	
Mean time to transition MFC 3 to 4: LI BSC	[redacted]	SE: 0.629 (Normal)		
Mean time to transition GMFC-MLD 4 to 5: LI BSC	[redacted]	SE: 0.629 (Normal)		
Mean time to transition GMFC-MLD 5 to 6: LI BSC	[redacted]	SE: 3.290 (Normal)	OSR-TIGET natural history data	
Mean time to transition GMFC-MLD 6 to Death: LI BSC	[redacted]	SE: 11.510 (Normal)	OSR-TIGET natural history data	
Mean time to transition GMFC-MLD 0 to 1: EJ BSC	58.3	SE: 0.24 (Normal)	Clinical assumption based on difference between 57 months. (average EJ onset occurring between 30 months and 7 years) and 45 months. (age at PS EJ model entry).	
Mean time to transition GMFC-MLD 1 to 2: EJ BSC	[redacted]	SE: 1.532 (Normal)	OSR-TIGET natural history data	
Mean time to transition GMFC-MLD 2 to 3: EJ BSC	[redacted]	SE: 0.417 (Normal)	OSR-TIGET natural history data for GMFC-MLD 2 to GMFC-MLD 5 split evenly between GMFC-MLD 2 to 3, GMFC-MLD 3 to 4 and GMFC-MLD 4 to 5	
Mean time to transition GMFC-MLD 3 to 4: EJ BSC	[redacted]	SE: 0.427 (Normal)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Mean time to transition GMFC-MLD 4 to 5: EJ BSC	[redacted]	SE: 0.417 (Normal)		
Mean time to transition GMFC-MLD 5 to 6: EJ BSC	[redacted]	SE: 2.960 (Normal)	OSR-TIGET natural history data	
Mean time to transition GMFC-MLD 6 to Death: EJ BSC	[redacted]	SE: 3.868 (Normal)	OSR-TIGET natural history data	
Percentage of full-responders: LI OTL-200	[redacted]	SE: 0.1333 (Beta)	OTL-200 Clinical trial data	
Time to progression (months): LI OTL-200	[redacted]	SE: 24 (Normal)	Clinical assumption reflecting lifetime benefit	
Progression Multiplier GMFC-MLD 0 to 1: LI OTL-200	[redacted]	SE: 0.1381 (Normal)	OTL-200 Clinical trial comparison of time to progression from GMFC-MLD 2 to GMFC-MLD 5 for OTL-200 partial-responders LI and EJ patients in the indicated population vs age- disease subtype matched patients in the natural history study	
Progression Multiplier GMFC-MLD 1 to 2: LI OTL-200	[redacted]	SE: 0.2915 (Normal)		
Progression Multiplier GMFC-MLD 2 to 3: LI OTL-200	[redacted]	SE: 0.5570 (Normal)		
Progression Multiplier GMFC-MLD 3 to 4: LI OTL-200	[redacted]	SE: 0.5570 (Normal)		
Progression Multiplier GMFC-MLD 4 to 5: LI OTL-200	[redacted]	SE: 0.5570 (Normal)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Progression Multiplier GMFC-MLD 5 to 6: LI OTL-200	[redacted]	SE: 0.5570 (Normal)		
Progression Multiplier GMFC-MLD 6 to Death: LI OTL-200	[redacted]	SE: 0.2 (Normal)	Clinical assumption – progression multiplier not applied to GMFC-MLD 6	
GMFC-MLD stage when partial responders stabilise: LI OTL-200	[redacted]	SE: 0.063 (Normal)	UK Structured Expert Elicitation (Orchard Data on file, 2020)	
Duration of stabilization: LI OTL-200 (years)	[redacted]	SE: 7.56 (Normal)		
Percentage of full-responders: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.16 (Beta)		
Time to progression (months): EJ Pre-symptomatic OTL-200	1200	SE: 24 (Normal)	OTL-200 Clinical trial data	
Progression Multiplier GMFC-MLD 0 to 1: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.1924 (Normal)	Clinical assumption reflecting lifetime benefit	
Progression Multiplier GMFC-MLD 1 to 2: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.1745 (Normal)	OTL-200 Clinical trial comparison of time to progression from GMFC-MLD 2 to GMFC-MLD 5 for OTL-200 partial-responders vs natural history patients in the combined LI and EJ dataset	
Progression Multiplier GMFC-MLD 2 to 3: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.5570 (Normal)		
Progression Multiplier GMFC-MLD 3 to 4: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.5570 (Normal)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Progression Multiplier GMFC-MLD 4 to 5: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.5570 (Normal)		
Progression Multiplier GMFC-MLD 5 to 6: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.5570 (Normal)		
Progression Multiplier GMFC-MLD 6 to Death: EJ Pre-symptomatic OTL-200	1.00	SE: 0.2 (Normal)		
Percentage of partial responders stabilizing at GMFC 1: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.136 (Beta)	Clinical assumption – progression multiplier not applied to GMFC-MLD 6	
GMFC-MLD stage when partial responders stabilise: EJ Pre-symptomatic OTL-200	[redacted]	SE: 0.10 (Normal)	UK Structured Expert Elicitation (Orchard Data on file, 2020)	
Duration of stabilization: EJ Pre-symptomatic OTL-200 (years)	[redacted]	SE: 7.56 (Normal)		
Percentage of full-responders: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.00 (Beta)		
Time to engraftment (months): EJ Early-symptomatic OTL-200	[redacted]	SE: 0.45 (Normal)	OTL-200 Clinical trial data	
Time to progression (months): EJ Early-symptomatic OTL-200	0	SE: 0.0 (Normal)	Based on clinical feedback of the time required from OTL-200 administration to engraftment and cross-correction	
Progression Multiplier GMFC-MLD 0 to 1: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.076 (Normal)	Lifetime retention of pre-symptomatic status not applicable for early-symptomatic EJ patients	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Progression Multiplier GMFC-MLD 1 to 2: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.0756 (Normal)	Based on clinical expert feedback, the mean time from GMFC-MLD 0 to 1 was assumed to be equal to the natural history	
Progression Multiplier GMFC-MLD 2 to 3: EJ Early-symptomatic OTL-200	[redacted]	SE: 1.286 (Normal)	UK Structured Expert Elicitation (Orchard Data on file, 2020)	
Progression Multiplier GMFC-MLD 3 to 4: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.327 (Normal)		
Progression Multiplier GMFC-MLD 4 to 5: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.327 (Normal)		
Progression Multiplier GMFC-MLD 5 to 6: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.076 (Normal)		
Progression Multiplier GMFC-MLD 6 to Death: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.076 (Normal)	Clinical assumption – progression multiplier not applied to GMFC-MLD 5	
Percentage of partial responders stabilizing: EJ Early-symptomatic OTL-200	[redacted]	SE: 0.089 (Beta)	Clinical assumption – progression multiplier not applied to GMFC-MLD 6	
GMFC-MLD stage when partial responders stabilise: EJ Early-symptomatic OTL-200	[redacted]	SE GMFC 1: 0.0378 (Normal) SE GMFC 2: 0.1134 (Normal)	UK Structured Expert Elicitation (Orchard Data on file, 2020)	
Duration of stabilization: EJ Early-symptomatic OTL-200 (years)	[redacted]	SE: 7.56 (Normal)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
CI, confidence interval; LI, Late Infantile; EJ, early juvenile; SE, standard error; GMFC-MLD, Gross Motor Function Classification-MLD; SEE, structured expert elicitation; BSC, Best supportive care				

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

A d*e novo* study estimated UK healthcare resource use (HCRU) costs associated with the management of MLD, based on aggregated data from n=6 clinical experts (October 2020). Details of the recruitment and inclusion criteria used to select the clinical experts are provided in the SEE study report. (Orchard Data on file, 2020)

Clinical experts

Six clinical experts were identified from all three lysosomal storage disorders reference centres in the UK, in which metachromatic leukodystrophy (MLD) patients are managed: St Mary's Children Hospital, Manchester; Great Ormond Street Hospital, London; and Birmingham Children's Hospital. Clinical experts were identified based on their expertise in MLD, or related disorders, and prior experience of treating MLD in UK clinical practice. Although none of the experts had direct experience of administering OTL-200 to patients, some were responsible for managing patients who had received treatment with OTL-200 as part of the clinical trials in Milan, Italy. Individuals were selected to best represent the range of healthcare professionals known to treat MLD and included paediatric haematologists, consultants in paediatric inherited metabolic diseases, and clinical neuropsychologists. Collectively, these experts were considered to provide good representation of the clinical expertise in MLD across the UK. The n=6 clinical experts included: Five consultant paediatric inherited metabolic diseases and one clinical neuropsychologist. Clinical experts were based in the Greater Manchester (n=1), Birmingham (n=1) and Greater London (n=4).

Methods

Each clinical expert took part in an individual, Excel-based worksheet, which quantified specific HCRU values using a prepared data summary sheet (Excel). Clinical experts were asked to provide information on the frequency and proportion of HCRU for MLD patients in each GMFC-MLD stage. Weighted means of proportions of patients using specific resources, frequency and where relevant, duration, of each type of resource used were calculated.

Unit costs sources

Multiple sources for unit costs were used to calculate costs associated with the HCRU identified:

- For inpatient hospitalisations, medical tests, medical visits, hospitalisations and GP & emergency costs, the source of unit costs was the NHS 2018/19 National Cost Collection data (National Health Service., 2019).
- For social services, the main source of unit costs was the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2019 report (Curtis and Burns, 2019).
- For drugs, the source of unit costs was the eMIT database for Pharmex products for 2019 (Department of Health and Social Care, 2019).
- For health material costs (e.g. wheelchairs, walkers, orthotics, etc.), costs were derived from unit costs reported in the National Schedule of NHS Costs (NHS trusts and NHS foundation trusts) for 2018-2019 (26) and the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2019 report (Curtis and Burns, 2019).

A summary of costs for MLD from UK HCRU study is presented in Table D22, Table D23 and Table D24 below and a cost calculator itemised underlying costs is provided in the Supplementary Medical Cost Calculator Excel document.

Table D22: Summary of monthly MLD-related medical costs for MLD from UK HCRU study (Ages 0-5)

Cost Category	Health State							
	State 0: Normal Development	**State 1: Symptom Onset**	**State 2: Early Disease Progression**	**State 3: Loss of Ambulation**	**State 4: Further Motor Function Loss**	**State 5: No Locomotion or Sitting**	**State 6: Complete Loss of Motor Function (Living at Home)**	**State 6: Complete Loss of Motor Function (In Hospital)**
Drugs	£0	£552	£717	£721	£721	£771	£754	N/A – Assumed to be included in hospitalisation costs
Medical tests	£0	£156	£74	£74	£74	£76	£74	
Medical visits	£0	£311	£307	£634	£680	£547	£558	
Hospitalizations	£49*	£0	£156	£262	£454	£535	£884	£14,199
GP & Emergency	£0	£9	£13	£15	£20	£23	£27	N/A – Assumed to be included in hospitalisation costs
Health material	£0	£34	£40	£76	£76	£91	£91	
Social services	£0	£0	£0	£0	£9,733	£9,838	£14,717	£9,120
Total	**£49**	**£1,062**	**£1,307**	**£1,784**	**£11,759**	**£11,880**	**£17,104**	**£23,319**

* In response to the ERG's suggestions in the clarification questions, the model has been updated to include MLD monitoring costs for the GMFC 0 patients until 18 years of age. This equates to 1 annual inpatient hospitalisation.

Table D23: Summary of monthly MLD-related medical costs for MLD from UK HCRU study (Ages 6-18)

Cost Category	Health State							
	State 0: Normal Development	**State 1: Symptom Onset**	**State 2: Early Disease Progression**	**State 3: Loss of Ambulation**	**State 4: Further Motor Function Loss**	**State 5: No Locomotion or Sitting**	**State 6: Complete Loss of Motor Function (Living at Home)**	**State 6: Complete Loss of Motor Function (In Hospital)**
Drugs	£0	£552	£717	£721	£721	£771	£754	N/A – Assumed to be included in hospitalisation costs
Medical tests	£0	£156	£74	£74	£74	£76	£74	
Medical visits	£0	£311	£307	£634	£680	£547	£558	
Hospitalizations	£49*	£0	£156	£262	£454	£535	£884	£14,199
GP & Emergency	£0	£9	£13	£15	£20	£23	£27	N/A – Assumed to be included in hospitalisation costs
Health material	£0	£34	£40	£76	£76	£91	£91	
Social services	£0	£0	£0	£0	£9,733	£9,838	£14,717	£9,120
Total	**£49**	**£1,062**	**£1,307**	**£1,784**	**£11,759**	**£11,880**	**£17,104**	**£23,319**

* In response to the ERG's suggestions in the clarification questions, the model has been updated to include MLD monitoring costs for the GMFC 0 patients until 18 years of age. This equates to 1 annual inpatient hospitalisation.

Table D24: Summary of monthly MLD-related medical costs for MLD from UK HCRU study (ages 19+)

Cost Category	Health State							
	State 0: Normal Development	**State 1: Symptom Onset**	**State 2: Early Disease Progression**	**State 3: Loss of Ambulation**	**State 4: Further Motor Function Loss**	**State 5: No Locomotion or Sitting**	**State 6: Complete Loss of Motor Function (Living at Home)**	**State 6: Complete Loss of Motor Function (In Hospital)**
Drugs	£0	£552	£717	£721	£721	£771	£754	N/A – Assumed to be included in hospitalisation costs
Medical tests	£0	£156	£74	£74	£74	£76	£74	
Medical visits	£0	£311	£307	£634	£680	£547	£558	
Hospitalizations	£0	£0	£156	£262	£454	£535	£884	£14,199
GP & Emergency	£0	£9	£13	£15	£20	£23	£27	N/A – Assumed to be included in hospitalisation costs
Health material	£0	£34	£40	£76	£76	£91	£91	
Social services	£0	£0	£0	£0	£9,928	£10,035	£15,011	£9,302
Total	**£0**	**£1,062**	**£1,307**	**£1,784**	**£11,954**	**£12,077**	**£17,398**	**£23,502**

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies

Resource use data for the NHS in England were identified using the search strategy outlined in the HRQL studies in Section 9.1. Eligibility criteria for these studies are specified in Section 11.1.2. As indicated earlier, no studies were identified.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[9].

As per Section 2.3.1, the de novo UK HCRU study included aggregated data from n=6 clinical experts to estimate HCRU associated with the management of MLD. Details of the recruitment and inclusion criteria used to select the clinical experts are provided in the UK SEE study report. (Orchard Data on file, 2020)

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The ex-factory (list) price for OTL-200 is £[redacted] per treatment.

12.3.5 If the list price is not used in the *de novo* cost- effectiveness model, provide the alternative price and a justification.

The list price is used in the de novo cost-effectiveness model. In addition, results are presented based on a has submitted a simple discount patient access scheme (PAS) of £[redacted] per treatment.

[9] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The total cost associated with the technology per treatment/patient (including the administration costs) for OTL-200 is £[redacted] using the OTL-200 list price and £[redacted] using the OTL-200 PAS price.

Table D25: Costs per treatment/patient associated with the technology (OTL-200) in the cost-effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	£[redacted] £[redacted]	List price for OTL-200. *PAS price for OTL-200.
Leukapheresis (cell harvest)	£4,272	Weighted average of HRGs for stem cell (SA34Z) and bone marrow harvest (SA18Z). National Reference costs – 2018/19
Conditioning	£7,899	Hospitalisation for conditioning (4 – 7 days) based on clinical opinion (Prof Rob Wynn) and SmPC. HRG for paediatric metabolic disorders hospitalisation non-elective inpatients (weighted average cost = £7,761) Busulfan costs = £138 per patient (eMIT 2019 database Busulfan 60mg vial – 8 pack = £367.81), average dose of Busulfan in clinical trials = 176.102mg
Administration and hospitalisation	£24,188	HRG paediatric metabolic disorders admissions weighted average elective inpatient (weighted average cost = £5,068). However, the SMPC states patient would stay about 4 – 12 weeks (average of 7.5 weeks) in the hospital, which is about 6 weeks longer than that reported for metabolic disorders inpatient admissions in Hospital Episode Statistics of 11 days (E75.2). The weighted average cost of elective inpatient excess bed day HRGs was calculated to be £460.73 (i.e. £5,068 /11). Thus overall hospital stay is calculated as £24,188 (i.e. £5068 + [41.5 x 460.73])
Follow-up transplant costs	£61,965	Hettle et al. (Hettle et al., 2017) – NICE Regenerative Medicines report. 2017. Follow-up costs for allogeneic stem cell transplants. Discharge to 6 months = £28,390, 6–12 months = £19,502, 12–24 months = £14,073. Expert opinion is follow-up for autologous transplants costs will be the same for allogeneic stem cell transplants, and patients will be discharged to metabolic care after 2 years.
Total Cost per treatment/patient	**£**[redacted] **£**[redacted]	Calculation *Calculation using OTL-200 PAS price.

Annual MLD care (i.e. HCRU) costs are not included in the total calculated costs for the technologies but are included in the model as health state costs. All costs for BSC are included in health state costs and have zero ‘technology’ costs.

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model

Table D26 shows the cost categories that are applied to each of the health states in the model. Section 2.2.6 and Section 2.3.1 show the unit cost data used in the model, and, for those costs which are cycle dependent, shows how the values were derived. Total costs by health state are shown in Section 2.5.8.

Table D26: List of health states and associated costs in the cost- effectiveness model

Cost categories	Health State						
	GMFC-MLD 0	**GMFC-MLD 1**	**GMFC-MLD 2**	**GMFC-MLD 3**	**GMFC-MLD 4**	**GMFC-MLD 5**	**GMFC-MLD 6**
Technology	OTL-200: all patients receive gene therapy at baseline.						
Technology administration	OTL-200: all patients incur administration costs at baseline as the technology is a one-time, single IV administration. Follow-up monitoring costs are also incurred over 2 years post-treatment.						
MLD treatment costs	GMFC-MLD 0 costs in each cycle times proportion of patients in the cycle	GMFC-MLD 1 costs in each cycle times proportion of patients in the cycle	GMFC-MLD 2 costs in each cycle times proportion of patients in the cycle	GMFC-MLD 3 costs in each cycle times proportion of patients in the cycle	GMFC-MLD 4 costs in each cycle times proportion of patients in the cycle	GMFC-MLD 5 costs in each cycle times proportion of patients in the cycle	Weighted average of GMFC-MLD 6 (At Home) vs GMFC-MLD 6 (In Hospital) costs. Costs applied in each cycle multiplied by the proportion of patients in the cycle

Adverse event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

As majority of the adverse events reported occurred within a short time following treatment and were mostly mild or moderate, it is assumed the costs of treating adverse events will be covered by the administration and follow-up costs Therefore these costs were not additionally included in the model.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state

The model captures all of the major costs and cost savings that arise with the introduction of OTL-200 in England within the base case. However, it is recognised that some of the cost savings associated with best supportive care (e.g. out of pocket costs that are borne by families and carers) may not be fully captured in this analysis.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The treatment benefit of OTL-200 is in halting or delaying disease progression, and evidence from the clinical trial and expert clinical opinion, suggests that a high proportion of patients stabilise on treatment (some stabilise earlier, whereas others later).

Compared to best supportive care, it is likely that treatment with OTL-200 results in downstream reductions in resource expenditure that would occur in the later stages of the disease. These costs can include adaptive beds, chest cough assist vests, and saliva suction machines. Costs for adapting vehicles, or the acquisition of vehicles such as Motability vehicles, associated with the later stages of disease, would also be reduced. Due to limited data on the

specific costs associated with home adaptations and the requirements for patients at specific points of the disease, this has not been taken into account in the cost-effectiveness model. However, it is estimated that adapted vehicles would cost around £10,000, and modifications to the home can cost in excess of £50,000. Any funding available for these adaptations is rarely sufficient to cover the full costs to the family, thereby creating a further financial burden on families. By delaying or preventing the progression to the later health states, OTL-200 can delay the point at which a wheelchair is required for patients, which is associated with significant replacement costs.

If children stabilise on OTL-200 treatment, this would increase the probability of parents returning to work and enhance career choices. (Pang et al., 2020) For patients themselves, there is a high chance of growing up to being economically productive and independent. This employment would enable patients and their caregivers to contribute to society through taxation, but this was not modelled due to limited data.

12.4 Approach to sensitivity analysis

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

The uncertainty around the values of parameter inputs has been investigated in deterministic and probabilistic sensitivity analyses, further details of which can be found in Section 12.4.3. In order to test the uncertainty around structural assumptions, scenario analyses were conducted, with particular inputs or assumptions being varied according to the scenario. A summary of these scenarios is provided in Table D27, with further details provided below.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated

Yes. Deterministic, probabilistic, and scenario-based sensitivity analyses were undertaken. The parameters used, together with the range of the variation (upper and lower values) and the method used, are summarised in Section 12.4.3.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

The values used for the parameters in the one-way sensitivity analysis are shown below in Table D27.

Table D27: Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base case value	Low Value	High Value
Combined MLD Population Weightings			
Proportion PS LI	[redacted]	[redacted]	[redacted]
Proportion PS EJ	[redacted]	[redacted]	[redacted]
Proportion ES EJ	[redacted]	[redacted]	[redacted]
Economic Inputs			
GMFC-MLD 0: medical cost (Age 0-5)	£49	£39	£58
GMFC-MLD 1: medical cost (Age 0-5)	£785.37	£628.30	£942.45
GMFC-MLD 2: medical cost (Age 0-5)	£897.44	£717.95	£1,076.92
GMFC-MLD 3: medical cost (Age 0-5)	£1,384.76	£1,107.81	£1,661.71
GMFC-MLD 4: medical cost (Age 0-5)	£1,636.26	£1,309.01	£1,963.51
GMFC-MLD 5: medical cost (Age 0-5)	£1,631.93	£1,305.54	£1,958.31
GMFC-MLD 6 (Living at home): medical cost (Age 0-5)	£4,573.30	£3,658.64	£5,487.96
GMFC-MLD 6 (In hospital): medical cost (Age 0-5)	£24,380.50	£19,504.40	£29,256.60
GMFC-MLD 0: medical cost (Age 6-18)	£49	£39	£58

GMFC-MLD 1: medical cost (Age 6-18)	£785.37	£628.30	£942.45
GMFC-MLD 2: medical cost (Age 6-18)	£897.44	£717.95	£1,076.92
GMFC-MLD 3: medical cost (Age 6-18)	£1,384.76	£1,107.81	£1,661.71
GMFC-MLD 4: medical cost (Age 6-18)	£1,636.26	£1,309.01	£1,963.51
GMFC-MLD 5: medical cost (Age 6-18)	£1,631.93	£1,305.54	£1,958.31
GMFC-MLD 6 (Living at home): medical cost (Age 6-18)	£4,573.30	£3,658.64	£5,487.96
GMFC-MLD 6 (In hospital): medical cost (Age 6-18)	£24,380.50	£19,504.40	£29,256.60
GMFC-MLD 0: medical cost (Age 19+)	£0	£0	£0
GMFC-MLD 1: medical cost (Age 19+)	£707.62	£566.10	£849.15
GMFC-MLD 2: medical cost (Age 19+)	£819.68	£655.75	£983.62
GMFC-MLD 3: medical cost (Age 19+)	£1,297.29	£1,037.83	£1,556.75
GMFC-MLD 4: medical cost (Age 19+)	£1,539.07	£1,231.26	£1,846.88
GMFC-MLD 5: medical cost (Age 19+)	£1,525.02	£1,220.01	£1,830.02
GMFC-MLD 6 (Living at home): medical cost (Age 19+)	£4,497.95	£3,598.36	£5,397.55
GMFC-MLD 6 (In hospital): medical cost (Age 19+)	£24,514.30	£19,611.44	£29,417.16
Percent GMFC-MLD 6 living at home	80%	64%	96%

OTL-200 one-time administration cost total	£[redacted]	£[redacted]	£[redacted]
OTL-200 2-year follow-up administration cost	£[redacted]	£[redacted]	£[redacted]
Clinical Inputs			
Time from GMFC-MLD 0 to 1: LI BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 1 to 2: LI BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 2 to 3: LI BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 3 to 4: LI BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 4 to 5: LI BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 5 to 6: LI BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 6 to Death: LI BSC	[redacted]	[redacted]	[redacted]
Percentage of full-responders: LI OTL-200	[redacted]	[redacted]	[redacted]
Time to progression: LI OTL-200	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 0 to 1: LI	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 1 to 2: LI	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 2 to 3: LI	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 3 to 4: LI	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 4 to 5: LI	[redacted]	[redacted]	[redacted]

Progression modifier GMFC-MLD 5 to 6: LI	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 6 to Death: LI	[redacted]	[redacted]	[redacted]
Percent of partial responders stabilising: OTL-200 LI	[redacted]	[redacted]	[redacted]
Duration of stabilisation: OTL-200 LI	100.00	80.00	120.00
Time from GMFC-MLD 0 to 1: EJ BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 1 to 2: EJ BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 2 to 3: EJ BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 3 to 4: EJ BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 4 to 5: EJ BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 5 to 6: EJ BSC	[redacted]	[redacted]	[redacted]
Time from GMFC-MLD 6 to Death: EJ BSC	[redacted]	[redacted]	[redacted]
Percentage of full-responders: EJ Pre-symptomatic OTL-200	[redacted]	[redacted]	[redacted]
Time to progression: EJ Pre-symptomatic OTL-200	1,200	960.00	1,440.00
Progression modifier GMFC-MLD 0 to 1: EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 1 to 2: EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 2 to 3: EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]

Progression modifier GMFC-MLD 3 to 4: EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 4 to 5: EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 5 to 6: EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 6 to Death: EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]
Percent of partial responders stabilising: OTL-200 EJ Pre-symptomatic	[redacted]	[redacted]	[redacted]
Duration of stabilisation: OTL-200 EJ Pre-symptomatic	100.00	80.00	120.00
Percentage of full-responders: EJ Early-symptomatic OTL-200	[redacted]	[redacted]	[redacted]
Time to engraftment (months): EJ Early-symptomatic OTL-200	[redacted]	[redacted]	[redacted]
Time to progression: EJ Early-symptomatic OTL-200	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 0 to 1: EJ Early-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 1 to 2: EJ Early-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 2 to 3: EJ Early-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 3 to 4: EJ Early-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 4 to 5: EJ Early-symptomatic	[redacted]	[redacted]	[redacted]
Progression modifier GMFC-MLD 5 to 6: EJ Early-symptomatic	[redacted]	[redacted]	[redacted]

Progression modifier GMFC-MLD 6 to Death: EJ Early-symptomatic	[redacted]	[redacted]	[redacted]
Percent of partial responders stabilizing: OTL-200 EJ Early-symptomatic	[redacted]	[redacted]	[redacted]
Duration of stabilization: OTL-200 EJ Early-symptomatic	100.00	80.00	120.00
Quality of life adjustments			
Utility: GMFC-MLD 1 (LI)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 2 (LI)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 3 (LI)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 4 (LI)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 5 (LI)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 6 (LI)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 1 (EJ Normal Cognition)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 2 (EJ Normal Cognition)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 3 (EJ Normal Cognition)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 4 (EJ Normal Cognition)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 5 (EJ Normal Cognition)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 6 (EJ Normal Cognition)	[redacted]	[redacted]	[redacted]

Utility: GMFC-MLD 0 (EJ Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 1 (EJ Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 2 (EJ Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 3 (EJ Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 4 (EJ Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 5 (EJ Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 6 (EJ Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 0 (EJ Severe Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 1 (EJ Severe Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 2 (EJ Severe Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 3 (EJ Severe Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 4 (EJ Severe Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 5 (EJ Severe Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Utility: GMFC-MLD 6 (EJ Severe Cognitive Impairment)	[redacted]	[redacted]	[redacted]
Caregiver disutility	[redacted]	[redacted]	[redacted]
Number of caregivers per patient: GMFC-MLD 0	0.00	0.00	0.00

Number of caregivers per patient: GMFC-MLD 1	0.00	0.00	0.00
Number of caregivers per patient: GMFC-MLD 2	0.00	0.00	0.00
Number of caregivers per patient: GMFC-MLD 3	0.00	0.00	0.00
Number of caregivers per patient: GMFC-MLD 4	0.00	0.00	0.00
Number of caregivers per patient: GMFC-MLD 5	2.00	1.60	2.40
Number of caregivers per patient: GMFC-MLD 6	2.00	1.60	2.40
Gen. Pop Utility (Ara and Brazier parameters): Percentage Male	0.49	0.40	0.59
EJ Cognitive Sub-state Distributions			
Time until cognitive decline (months) (BSC)	12	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]

GMFC-MLD 1: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Normal Cognition (BSC)	[redacted]	[redacted]	[redacted]

GMFC-MLD 6: Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Severe Cognitive Impairment (BSC)	[redacted]	[redacted]	[redacted]
Time until cognitive decline (months) (OTL-200 Pre-symptomatic Full Responder)	147	117.6	176.4
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	1.00	1.00	1.00
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	1.00	1.00	1.00
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 1: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	1.00	1.00	1.00
GMFC-MLD 1: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00

GMFC-MLD 2: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	1.00	1.00	1.00
GMFC-MLD 2: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 3: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	1.00	1.00	1.00
GMFC-MLD 3: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 4: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	1.00	1.00	1.00
GMFC-MLD 4: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0.00	0.00	0.00
GMFC-MLD 5: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
Time until cognitive decline (months) (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	1.00	1.00	1.00
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	0.00	0.00	0.00
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	0.00	0.00	0.00
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 1: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
Time until cognitive decline (months) (OTL-200 Symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Normal Cognition (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Early-symptomatic Full Responder)	[redacted]	[redacted]	[redacted]
Time until cognitive decline (months) (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 2: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Normal Cognition (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]

GMFC-MLD 6: Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Early-symptomatic Partial Responder)	[redacted]	[redacted]	[redacted]

Multi-way sensitivity analysis

The impact of varying multiple parameters simultaneously for OTL-200 versus best supportive care was explored in the form of a number of scenario analyses, which are detailed in Table D28.

Table D28: Modelled exploratory scenario descriptions

Scenario Description	Base Case Values	Scenario Values: Lower limit	Scenario Values: Upper limit
Discount Rate			
Discount Rate for costs and benefits	Discount Rate: 1.5%	Discount Rate: **0%**	Discount Rate: **3.5%**
Caregiver Disutility			
Number of caregivers required for caregiver disutility	Caregivers Required: GMFC-MLD 2: 0 GMFC-MLD 3: 0 GMFC-MLD 4: 0 GMFC-MLD 5: 2 GMFC-MLD 6: 2	Caregivers Required: GMFC-MLD 2: 0 GMFC-MLD 3: 0 GMFC-MLD 4: 0 GMFC-MLD 5: 2 GMFC-MLD 6: 2	Caregivers Required: GMFC-MLD 2: **0.5** GMFC-MLD 3: **0.5** GMFC-MLD 4: **1** GMFC-MLD 5: 2 GMFC-MLD 6: 2
Time to Engraftment			
Time to engraftment	ES EJ time to engraftment: 6 months	ES EJ time to engraftment: **0 months**	ES EJ time to engraftment: **12 months**

Scenario Description	Base Case Values	Scenario Values: Lower limit	Scenario Values: Upper limit
for ES EJ cohort			
Full/Partial Responder Breakdowns			
Full-Responder and Partial-Responders Partial Responders stabilising at either GMFC-MLD 1 or 2 or progressing at slower rate than NHx			

Scenario Description	Base Case Values			Scenario Values: Lower limit			Scenario Values: Upper limit		
Progression Modifiers (PM)*									
Progression modifiers (from GMFC-MLD 0 to GMFC-MLD 6)	PS LI PMs by GMFC-MLD:	PS EJ PMs by GMFC-MLD:	ES EJ PMs by GMFC-MLD:	PS LI PMs by GMFC-MLD:	PS EJ PMs by GMFC-MLD:	ES EJ PMs by GMFC-MLD:	PS LI PMs by GMFC-MLD:	PS EJ PMs by GMFC-MLD:	ES EJ PMs by GMFC-MLD:
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of Combined MLD Population									
Proportion of disease variant in MLD combined population	[redacted]			[redacted]			[redacted]		

Scenario Description	Base Case Values	Scenario Values: Lower limit	Scenario Values: Upper limit
Natural history Source Data			
Natural history source data for LI and EJ using Elgun, 2019	Source: OSR-TIGET Natural history Study	Source: **Elgun, 2019 publication**	Source: **Kehrer, 2011 publication**

Note: **Bold** values represent modifications from the base case
*PM values presented in order from GMFC-MLD 0 to GMFC-MLD 6.

Probabilistic sensitivity analysis

Parameters included in the probabilistic sensitivity analysis (PSA) are shown below in Table D29.

Table D29: Parameter values used in probabilistic sensitivity analysis

Variable	Base case value	Distribution
Combined MLD Population: Proportion of PS LI Patients	[redacted]	Dirichlet
Combined MLD Population: Proportion of PS EJ Patients	[redacted]	
Combined MLD Population: Proportion of ES EJ Patients	[redacted]	
GMFC-MLD 0 total (Age 0 – 5)	£49	Gamma
GMFC-MLD 1 total (Age 0 – 5)	785.37	

Variable	Base case value	Distribution
GMFC-MLD 2 total (Age 0 – 5)	£897.44	
GMFC-MLD 3 total (Age 0 – 5)	£1,384.76	
GMFC-MLD 4 total (Age 0 – 5)	£1,636.26	
GMFC-MLD 5 total (Age 0 – 5)	£1,631.93	
GMFC-MLD 6 (At Home) total (Age 0 – 5)	£4,573.30	
GMFC-MLD 6 (In Hospital) total (Age 0 – 5)	£24,380.50	
GMFC-MLD 0 total (Age 6 – 18)	£49	
GMFC-MLD 1 total (Age 6 – 18)	£897.44	
GMFC-MLD 2 total (Age 6 – 18)	£1,384.76	
GMFC-MLD 3 total (Age 6 – 18)	£1,636.26	
GMFC-MLD 4 total (Age 6 – 18)	£1,631.93	
GMFC-MLD 5 total (Age 6 – 18)	£4,573.30	
GMFC-MLD 6 (At Home) total (Age 6 – 18)	£24,380.50	
GMFC-MLD 6 (In Hospital) total (Age 6 – 18)	£897.44	
GMFC-MLD 0 total (Age 19+)	£0	

Variable	Base case value	Distribution
GMFC-MLD 1 total (Age 19+)	£707.62	
GMFC-MLD 2 total (Age 19+)	£819.68	
GMFC-MLD 3 total (Age 19+)	£1,297.29	
GMFC-MLD 4 total (Age 19+)	£1,539.07	
GMFC-MLD 5 total (Age 19+)	£1,525.02	
GMFC-MLD 6 (At Home) total (Age 19+)	£4,497.95	
GMFC-MLD 6 (In Hospital) total (Age 19+)	£24,514.30	
Percentage of GMFC-MLD 6 patients living at home (vs. in hospital)	80%	Beta
OTL-200 administration: Leukapheresis (cell harvest)	£4,272	Gamma
OTL-200 administration: Conditioning	£7,899	
OTL-200 administration: Administration and hospitalisation	£24,188	
OTL-200 administration: Follow-up transplant costs	£61,965	
Utility: GMFC-MLD 0 (EJ Cognitive Impairment)	0.75	Normal
Utility: GMFC-MLD 0 (EJ Severe Cognitive Impairment)	0.46	
Utility: GMFC-MLD 1 (LI)	[redacted]	

Variable	Base case value	Distribution
Utility: GMFC-MLD 1 (EJ Normal Cognition)	[redacted]	
Utility: GMFC-MLD 1 (EJ Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 1 (EJ Severe Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 2 (LI)	[redacted]	
Utility: GMFC-MLD 2 (EJ Normal Cognition)	[redacted]	
Utility: GMFC-MLD 2 (EJ Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 2 (EJ Severe Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 3 (LI)	[redacted]	
Utility: GMFC-MLD 3 (EJ Normal Cognition)	[redacted]	
Utility: GMFC-MLD 3 (EJ Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 3 (EJ Severe Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 4 (LI)	[redacted]	
Utility: GMFC-MLD 4 (EJ Normal Cognition)	[redacted]	
Utility: GMFC-MLD 4 (EJ Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 4 (EJ Severe Cognitive Impairment)	[redacted]	

Variable	Base case value	Distribution
Utility: GMFC-MLD 5 (LI)	[redacted]	
Utility: GMFC-MLD 5 (EJ Normal Cognition)	[redacted]	
Utility: GMFC-MLD 5 (EJ Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 5 (EJ Severe Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 6 (LI)	[redacted]	
Utility: GMFC-MLD 6 (EJ Normal Cognition)	[redacted]	
Utility: GMFC-MLD 6 (EJ Cognitive Impairment)	[redacted]	
Utility: GMFC-MLD 6 (EJ Severe Cognitive Impairment)	[redacted]	
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): % male in equation	[redacted]	Beta
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation intercept	[redacted]	Normal
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation sex coefficient	[redacted]	
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation age coefficient	[redacted]	
Utility GMFC-MLD 0 (LI/EJ Normal Cognition): equation age^2 coefficient	[redacted]	
Disutility: Caregiver Disutility	[redacted]	
Caregiver Disutility: Number of Caregiver (GMFC-MLD 0)	0	

Variable	Base case value	Distribution
Caregiver Disutility: Number of Caregiver (GMFC-MLD 1)	0	
Caregiver Disutility: Number of Caregiver (GMFC-MLD 2)	0	
Caregiver Disutility: Number of Caregiver (GMFC-MLD 3)	0	
Caregiver Disutility: Number of Caregiver (GMFC-MLD 4)	0	
Caregiver Disutility: Number of Caregiver (GMFC-MLD 5)	2	
Caregiver Disutility: Number of Caregiver (GMFC-MLD 6)	2	
Time until cognitive decline (months) (BSC)	12	
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (BSC)	[redacted]	
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (BSC)	[redacted]	Dirichlet
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (BSC)	[redacted]	
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (BSC)	[redacted]	Dirichlet
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 1: Normal Cognition (BSC)	[redacted]	
GMFC-MLD 1: Cognitive Impairment (BSC)	[redacted]	Dirichlet

Variable	Base case value	Distribution
GMFC-MLD 1: Severe Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 2: Normal Cognition (BSC)	[redacted]	Dirichlet
GMFC-MLD 2: Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 2: Severe Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 3: Normal Cognition (BSC)	[redacted]	Dirichlet
GMFC-MLD 3: Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 3: Severe Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 4: Normal Cognition (BSC)	[redacted]	Dirichlet
GMFC-MLD 4: Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 4: Severe Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 5: Normal Cognition (BSC)	[redacted]	Dirichlet
GMFC-MLD 5: Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 5: Severe Cognitive Impairment (BSC)	[redacted]	
GMFC-MLD 6: Normal Cognition (BSC)	[redacted]	Dirichlet
GMFC-MLD 6: Cognitive Impairment (BSC)	[redacted]	

Variable	Base case value	Distribution
GMFC-MLD 6: Severe Cognitive Impairment (BSC)	[redacted]	
Time until cognitive decline (months) (OTL-200 Pre-symptomatic Full Responder)	147	Normal
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 1: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 1: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 2: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 2: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 3: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	Dirichlet

Variable	Base case value	Distribution
GMFC-MLD 3: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 4: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	100%	
GMFC-MLD 4: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	Dirichlet
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 5: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	0%	
GMFC-MLD 5: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	8%	Dirichlet
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	21%	
GMFC-MLD 6: Normal Cognition (OTL-200 Pre-symptomatic Full Responder)	71%	
GMFC-MLD 6: Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	0%	Dirichlet
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Full Responder)	14%	
Time until cognitive decline (months) (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Normal
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	

Variable	Base case value	Distribution
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 1: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 1: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 2: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 2: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 3: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 3: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 4: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 4: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	

Variable	Base case value	Distribution
GMFC-MLD 5: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 5: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 6: Normal Cognition (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 6: Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Pre-symptomatic Partial Responder)	[redacted]	
Time until cognitive decline (months) (OTL-200 Symptomatic Full Responder)	112	Normal
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 1: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 1: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	

Variable	Base case value	Distribution
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 2: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 2: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 3: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 3: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 4: Normal Cognition (OTL-200 Symptomatic Full Responder)	100%	Dirichlet
GMFC-MLD 4: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	0%	
GMFC-MLD 5: Normal Cognition (OTL-200 Symptomatic Full Responder)	8%	Dirichlet
GMFC-MLD 5: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	21%	
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	71%	
GMFC-MLD 6: Normal Cognition (OTL-200 Symptomatic Full Responder)	0%	Dirichlet
GMFC-MLD 6: Cognitive Impairment (OTL-200 Symptomatic Full Responder)	14%	

Variable	Base case value	Distribution
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Symptomatic Full Responder)	86%	
Time until cognitive decline (months) (OTL-200 Symptomatic Partial Responder)	[redacted]	Normal
GMFC-MLD 0 Before Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 0 Before Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 0 Before Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 0 After Cognitive Decline: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 0 After Cognitive Decline: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 0 After Cognitive Decline: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 1: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 1: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 1: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 2: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 2: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 2: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 3: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet

Variable	Base case value	Distribution
GMFC-MLD 3: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 3: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 4: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 4: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 4: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 5: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 5: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 5: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 6: Normal Cognition (OTL-200 Symptomatic Partial Responder)	[redacted]	
GMFC-MLD 6: Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	Dirichlet
GMFC-MLD 6: Severe Cognitive Impairment (OTL-200 Symptomatic Partial Responder)	[redacted]	
Mean time to transition GMFC-MLD 0 to 1: LI BSC	[redacted]	
Mean time to transition GMFC-MLD 1 to 2: LI BSC	[redacted]	Normal
Mean time to transition GMFC-MLD 2 to 3: LI BSC	[redacted]	
Mean time to transition GMFC-MLD 3 to 4: LI BSC	[redacted]	

Variable	Base case value	Distribution
Mean time to transition GMFC-MLD 4 to 5: LI BSC	[redacted]	
Mean time to transition GMFC-MLD 5 to 6: LI BSC	[redacted]	
Mean time to transition GMFC-MLD 6 to Death: LI BSC	[redacted]	
Mean time to transition GMFC-MLD 0 to 1: EJ BSC	[redacted]	
Mean time to transition GMFC-MLD 1 to 2: EJ BSC	[redacted]	
Mean time to transition GMFC-MLD 2 to 3: EJ BSC	[redacted]	
Mean time to transition GMFC-MLD 3 to 4: EJ BSC	[redacted]	
Mean time to transition GMFC-MLD 4 to 5: EJ BSC	[redacted]	
Mean time to transition GMFC-MLD 5 to 6: EJ BSC	[redacted]	
Mean time to transition GMFC-MLD 6 to Death: EJ BSC	[redacted]	
Percentage of full-responders: LI OTL-200	[redacted]	Beta
Time to progression (months): LI OTL-200	[redacted]	Normal
Progression Multiplier GMFC-MLD 0 to 1: LI OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 1 to 2: LI OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 2 to 3: LI OTL-200	[redacted]	

Variable	Base case value	Distribution
Progression Multiplier GMFC-MLD 3 to 4: LI OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 4 to 5: LI OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 5 to 6: LI OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 6 to Death: LI OTL-200	[redacted]	
GMFC-MLD stage when partial responders stabilise: LI OTL-200	[redacted]	Normal
Duration of stabilization: LI OTL-200 (years)	[redacted]	Normal
Percentage of full-responders: EJ Pre-symptomatic OTL-200	[redacted]	Beta
Time to progression (months): EJ Pre-symptomatic OTL-200	[redacted]	Normal
Progression Multiplier GMFC-MLD 0 to 1: EJ Pre-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 1 to 2: EJ Pre-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 2 to 3: EJ Pre-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 3 to 4: EJ Pre-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 4 to 5: EJ Pre-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 5 to 6: EJ Pre-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 6 to Death: EJ Pre-symptomatic OTL-200	[redacted]	

Variable	Base case value	Distribution
Percentage of partial responders stabilising at GMFC 1: EJ Pre-symptomatic OTL-200	[redacted]	Beta
GMFC-MLD stage when partial responders stabilise: EJ Pre-symptomatic OTL-200	[redacted]	Normal
Duration of stabilisation: EJ Pre-symptomatic OTL-200 (years)	[redacted]	Normal
Percentage of full-responders: EJ Early-symptomatic OTL-200	[redacted]	Beta
Time to engraftment (months): EJ Early-symptomatic OTL-200	[redacted]	Normal
Time to progression (months): EJ Early-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 0 to 1: EJ Early-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 1 to 2: EJ Early-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 2 to 3: EJ Early-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 3 to 4: EJ Early-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 4 to 5: EJ Early-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 5 to 6: EJ Early-symptomatic OTL-200	[redacted]	
Progression Multiplier GMFC-MLD 6 to Death: EJ Early-symptomatic OTL-200	[redacted]	
Percentage of partial responders stabilising: EJ Early-symptomatic OTL-200	[redacted]	Beta
Duration of stabilization: EJ Early-symptomatic OTL-200 (years)	[redacted]	Normal

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Not applicable. All relevant parameters were included in the one-way, multi-way, scenario and probabilistic sensitivity analyses as described in Section 2.4.3.

12.5 Results of economic analysis

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

In the base case for the combined cohort, the incremental cost-effectiveness ratio for OTL-200 versus BSC is £[redacted] per QALY gained using the OTL-200 ex-factory (list) price and £[redacted] per QALY gained using the OTL-200 PAS price. The incremental costs and outcomes in the form of life years and QALYs are presented in Table D30. The analyses in the base case have been discounted at 1.5% for costs and outcomes.

Table D30: Base case results (combined MLD cohort)

Technologies	Total lifetime costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
OTL-200 (at the List Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200 (at the PAS Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	**£782,541**	**13.0**	**-4.61**	**N/A**	**N/A**	**N/A**	**N/A**

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; BSC, Best supportive care; PAS, Patient access scheme
Costs and benefits discounted at 1.5%

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Beyond the first year of the clinical trial, clinical trial estimates are influenced by the patients lost to follow up given the variable follow-up duration in the OTL-200 clinical trial. Due to the variability in the cohort size over time in the clinical trial, which is not present in the economic model as the partitioned survival model tracks a homogenous cohort over time, one-to-one comparisons between the clinical trial and economic model can only be made in the first-year post-treatment without including assumptions regarding the censored patients expected disease progression/stabilisation. Some clinical trial patients may experience stabilisation in GMFC-MLD 3 or 4 if they were observed over a longer follow-up period, however, only the stabilisation that was observed to occur in the clinical trial was used to inform the model inputs. Additionally, economic model incorporates all-cause mortality in all GMFC-MLD stages and therefore would present a conservative mortality estimate of when compared to the clinical trial during the first 5-years post-treatment.

Comparing the clinical trial and economic model estimates in the first-year post-treatment show a relatively consistent alignment between the proportions of patients in each GMFC-MLD state, especially given the small sample sizes of the OTL-200 trial populations and use of averages to estimate disease progression. The slight deviation in the first year for the PS-EJ population was due to a single patient death within the first year of their initial reported GMFC-MLD score. The progression of this patient greatly differed from the progression presented in the EJ natural history and was conservatively modelled to include progressing non-stabilising patients. Tables D31-D33 compare the clinical trial results with the model results for each GMFC-MLD state for PS-LI, PS-EJ and ES-EJ MLD.

Table D31: Summary of model results compared with clinical data (PS-LI)

	GMFC-MLD 0		GMFC-MLD 1		GMFC-MLD 2		GMFC-MLD 3		GMFC-MLD 4		GMFC-MLD 5		GMFC-MLD 6	
	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result
At 1 year post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 2 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 3 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 4 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 5 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: 'Trial result' data based on Orchard Therapeutics OTL-200 clinical trial data for the PS-LI patient population. Model result percentages may not add to 100% because of rounding and proportion of patients estimated to die not presented in this table.

Table D32: Summary of model results compared with clinical trial data (PS-EJ Population)

	GMFC-MLD 0		GMFC-MLD 1		GMFC-MLD 2		GMFC-MLD 3		GMFC-MLD 4		GMFC-MLD 5		GMFC-MLD 6	
	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result
At 1 year post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 2 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 3 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 4 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 5 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: 'Trial result' data based on Orchard Therapeutics OTL-200 clinical trial data for the PS-EJ patient population. Model result percentages may not add to 100% because of rounding and proportion of patients estimated to die not presented in this table.
*1 patient reported a death and was not categorised into a health state but still considered for the eligible population 1-year post-treatment

Table D33: Summary of model results compared with clinical trial data (ES-EJ Population)

	GMFC-MLD 0		GMFC-MLD 1		GMFC-MLD 2		GMFC-MLD 3		GMFC-MLD 4		GMFC-MLD 5		GMFC-MLD 6	
	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result	Trial Result (n)	Model Result
At 1 year post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 2 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 3 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 4 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At 5 years post-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: ‘Trial result’ data based on Orchard Therapeutics OTL-200 clinical trial data for the ES-EJ patient population. Model result percentages may not add to 100% because of rounding and proportion of patients estimated to die not presented in this table

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator

Table D34 shows the probability of a patient being in one of the surviving health states or death over time.

Table D34: Probability of a patient being in surviving health states or death over the lifetime of the model by intervention arm (Combined Cohort)

Patients who received OTL-200								
Year after treatment	**GMFC-MLD 0**	**GMFC-MLD 1**	**GMFC-MLD 2**	**GMFC-MLD 3**	**GMFC-MLD 4**	**GMFC-MLD 5**	**GMFC-MLD 6**	**Dead**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received BSC								
Year after treatment	**GMFC-MLD 0**	**GMFC-MLD 1**	**GMFC-MLD 2**	**GMFC-MLD 3**	**GMFC-MLD 4**	**GMFC-MLD 5**	**GMFC-MLD 6**	**Dead**
1	45.63%	23.37%	10.60%	9.23%	6.22%	4.31%	0.62%	0.01%
5	15.11%	7.18%	2.13%	2.36%	2.64%	17.44 %	47.66%	5.49%
10	5.36%	2.52%	0.72%	0.79%	0.86%	8.22%	53.41%	28.12%
25	0.24%	0.11%	0.03%	0.04%	0.04%	0.43%	7.28%	91.82%
50	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	99.99%
75	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00 %
100	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	100.00 %

Abbreviations: BSC=best supportive care

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table D35 shows QALYs accrued over time for a patient treated with OTL-200 or BSC. Note that this is based on the probability of the patient being in each of the health states in each time period. QALYs are discounted at 1.5%.

Table D35: QALYs accrued over time for a patient based on the probability of being in each health state in each time period (discounted at 1.5%) (Combined Cohort)

Patients who received OTL-200								
Year after treatment	**GMFC-MLD 0**	**GMFC-MLD 1**	**GMFC-MLD 2**	**GMFC-MLD 3**	**GMFC-MLD 4**	**GMFC-MLD 5**	**GMFC-MLD 6**	**Total**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received BSC								
Year after treatment	**GMFC-MLD 0**	**GMFC-MLD 1**	**GMFC-MLD 2**	**GMFC-MLD 3**	**GMFC-MLD 4**	**GMFC-MLD 5**	**GMFC-MLD 6**	**Total**
1	0.57	0.20	0.04	0.00	-0.01	-0.01	0.00	**0.80**
5	1.52	0.59	0.14	0.00	-0.08	-0.63	-0.99	**0.56**
10	1.84	0.72	0.17	0.00	-0.11	-0.98	-2.81	**-1.16**
25	2.02	0.79	0.19	0.00	-0.12	-1.26	-6.08	**-4.45**
50	2.03	0.79	0.19	0.00	-0.12	-1.27	-6.24	**-4.61**
75	2.03	0.79	0.19	0.00	-0.12	-1.27	-6.24	**-4.61**
100	2.03	0.79	0.19	0.00	-0.12	-1.27	-6.24	**-4.61**

Abbreviations: BSC=best supportive care

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

The disaggregation of accrued LYs and QALYs is presented in

Table D36. Note that these outcomes are discounted at 1.5% and with half cycle correction.

Table D36: Model outputs by outcomes (discounted at 1.5%) (Combined Cohort)

Patients who received OTL-200		
Outcome	**Life years**	**QALYs**
GMFC-MLD 0	[redacted]	[redacted]
GMFC-MLD 1	[redacted]	[redacted]
GMFC-MLD 2	[redacted]	[redacted]
GMFC-MLD 3	[redacted]	[redacted]
GMFC-MLD 4	[redacted]	[redacted]
GMFC-MLD 5	[redacted]	[redacted]
GMFC-MLD 6	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]
Patients who received BSC		
Outcome	**Life years**	**QALYs**
GMFC-MLD 0	2.23	2.03
GMFC-MLD 1	1.05	0.79
GMFC-MLD 2	0.35	0.19
GMFC-MLD 3	0.35	0.00
GMFC-MLD 4	0.35	-0.12
GMFC-MLD 5	1.63	-1.27
GMFC-MLD 6	7.07	-6.24
TOTAL	**13.0**	**-4.61**

Abbreviations: BSC= best supportive care; LYG,=life years gained; QALYs,=quality-adjusted life years.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below

The disaggregation of incremental QALYs by health state are presented in Table D37. OTL-200 provides an incremental QALY gain: of [redacted] QALYs when compared with BSC.

Table D37: Summary of QALY gain differences by health state (OTL-200 versus BSC) – discounted (Combined Cohort)

Outcome	QALYs OTL-200	QALYs BSC	Increment	Absolute increment	% absolute increment
GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Discounted at 1.5% for benefits
Abbreviations: BSC,=best supportive care; QALYs,=quality-adjusted life years

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

Table D38 shows the undiscounted incremental QALYs for OTL-200 compared with best supportive care (BSC).

Table D38: Undiscounted incremental QALYs gained for OTL-200 compared with best supportive care (BSC) (Combined Cohort)

Intervention	QALYs from intervention	Incremental QALYs (OTL-200 over comparator)
OTL-200	[redacted]	[redacted]
BSC	-5.75	[redacted]

Abbreviations: BSC=best supportive care; N/A=not applicable; QALYs=quality-adjusted life years.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table D12.

Table D39 and Table D41 show the costs of OTL-200 and BSC by category of costs for the OTL-200 ex-factory (list) price and PAS price. Of the absolute

incremental costs, between 83% to 84% are for the technology cost of OTL-200 with between 13% and 24% accounting for decreases in MLD treatment/care costs for patients (mainly due to protraction or prevention of MLD disease progression), depending if the ex-factory (list) price or PAS price are utilised.

Table D40: Costs of OTL-200 at ex-factory (list) price and best supportive care (BSC) by category of cost (discounted at 1.5%)† (Combined Cohort)

Item	Cost OTL-200	Cost BSC	Increment	Absolute increment	% absolute increment
Technology cost (list price)	[redacted]	£0	[redacted]	[redacted]	[redacted]
Administration cost of the technology	£97,859	£0	£97,859	£97,859	[redacted]
Mean total MLD treatment cost (all care costs)	£333,857	£782,525	-£448,669	£448,669	[redacted]
Total	[redacted]	£782,525	[redacted]	[redacted]	[redacted]

Abbreviations: BSC,=best supportive care; MLD=metachromatic leukodystrophy. † Values are reported as per the economic model; discrepancies are due to rounding.

Table D41: Costs of OTL-200 at Patient Access Scheme (PAS) price and best supportive care (BSC) by category of cost (OTL-200 versus BSC) (discounted at 1.5%)† (Combined Cohort)

Item	Cost OTL-200	Cost BSC	Increment	Absolute increment	% absolute increment
Technology cost (PAS price)	[redacted]	£0	[redacted]	[redacted]	[redacted]
Administration cost of the technology	£97,859	£0	£97,859	£97,859	[redacted]
Mean total MLD treatment cost (all care costs)	£333,857	£782,525	-£448,669	£448,669	[redacted]
Total	[redacted]	£782,525	[redacted]	[redacted]	[redacted]

Abbreviations: BSC,=best supportive care; MLD,=metachromatic leukodystrophy; PAS = patient access scheme. † Values are reported as per the economic model; discrepancies are

due to rounding.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Table D42 and Table D43 show the total costs for OTL-200 by health state versus best supportive care (BSC) for the OTL-200 ex-factory (list) price and patient access scheme (PAS) price. Note that costs for the technology (OTL-200) include the costs of the technology (drug acquisition and administration costs) and MLD-related care costs incurred whilst in the health state.

Note also that since OTL-200 is a one-time, single IV treatment, costs of the technology (drug acquisition and administration costs) were applied at the entry into the model. For early-symptomatic EJ patients, 40% enter the model at GMFC-MLD 0 and 60% enter at GMFC-MLD 1 with the costs of the technology allocated accordingly.

Table D42: Total costs of OTL-200 at ex-factory (list) price and BSC by health state (discounted at 1.5%) (Combined Cohort)

Health state	Cost OTL-200 (£)	Cost BSC (£)	Increment	Absolute increment	% absolute increment
GMFC-MLD 0	[redacted]	1,264	[redacted]	[redacted]	[redacted]
GMFC-MLD 1	[redacted]	9,882	[redacted]	[redacted]	[redacted]
GMFC-MLD 2	[redacted]	3,760	[redacted]	[redacted]	[redacted]
GMFC-MLD 3	[redacted]	5,772	[redacted]	[redacted]	[redacted]
GMFC-MLD 4	[redacted]	6,782	[redacted]	[redacted]	[redacted]
GMFC-MLD 5	[redacted]	31,652	[redacted]	[redacted]	[redacted]
GMFC-MLD 6	[redacted]	723,429	[redacted]	[redacted]	[redacted]
Total	[redacted]	**782,541**	[redacted]	[redacted]	[redacted]

Abbreviations: BSC=best supportive care. Figures may not sum exactly due to rounding during OTL-200 apportioning between states.

Table D43: Total costs of OTL-200 at Patient Access Scheme (PAS) price and BSC by health state (discounted at 1.5%) (Combined Cohort)

Health state	Cost OTL-200 (£)	Cost BSC (£)	Increment	Absolute increment	% absolute increment
GMFC-MLD 0	[redacted]	1,264	[redacted]	[redacted]	[redacted]
GMFC-MLD 1	[redacted]	9,882	[redacted]	[redacted]	[redacted]
GMFC-MLD 2	[redacted]	3,760	[redacted]	[redacted]	[redacted]
GMFC-MLD 3	[redacted]	5,772	[redacted]	[redacted]	[redacted]
GMFC-MLD 4	[redacted]	6,782	[redacted]	[redacted]	[redacted]
GMFC-MLD 5	[redacted]	31,652	[redacted]	[redacted]	[redacted]
GMFC-MLD 6	[redacted]	723,429	[redacted]	[redacted]	[redacted]
Total	[redacted]	**782,541**	[redacted]	[redacted]	[redacted]

Abbreviations: BSC,=best supportive care. Figures may not sum exactly due to rounding during OTL-200 apportioning between states.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Adverse events are not included in the model for the reasons mentioned in Section 12.3.5.1.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in Table D10.1.

[redacted] shows the impact on the ICER from the one-way sensitivity analysis for OTL-200 versus BSC: results in table format are shown in [redacted]. All parameters were varied by +/- 20% or natural limits if these were within the +/- 20% range.

Figure D7: [redacted]

Table D44: [redacted]

Impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (OTL-200 versus BSC) – top 20 results only (Combined Cohort)

Rank	Parameter Description	Lower limit	Higher limit	ICER (Low cost limit)	ICER (High cost limit)	Range	Lower limit % Change	Higher limit % Change
1	Percentage of ES EJ OTL-200 partial responder patients who stabilise at GMFC 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Percentage of PS EJ OTL-200 Full Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Percentage of PS LI OTL-200 Full Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Percentage of PS LI patients in GMFC 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Percentage of PS EJ OTL200 partial responder patients who stabilise at GMFC 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Percentage of PS LI OTL200 Partial Responder patients who stabilise at GMFC 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	BSC: Median time spent in GMFC 0 to 1 in EJ patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Utility value for PS LI patients in GMFC 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	GMFC-MLD 2 Medical Cost (Age 19+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	BSC: Median time spent in GMFC 1 to 2 in EJ patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Percentage of PS LI OTL-200 Partial Responders who stabilise in GMFC 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	Utility value for PS LI patients in GMFC 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	Cost of OTL-200 administration in hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14	GMFC-MLD 1 Medical Cost (Age 19+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	Time to progression for OTL-200 PS LI patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	Mortality for EJ patients in GMFC 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	BSC: Median time spent in GMFC 0 to 1 in PS LI patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	Total Cost of OTL-200 administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	GMFC-MLD 2 Medical Cost (Age 6-18)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	Rate of progression for OTL-200 PS EJ patients from GMFC 0 to GMFC 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Table D45 presents further sensitivity analyses. Results show the impact of changing parameter values on discount rate, progression modifiers, engraftment time, caregiver disutility values, responder status, and distribution of patients in the combined cohort.

These sensitivity analyses and scenarios are described in more detail in Section 12.4.3.2 and the results are discussed in Section 12.5.2.4.

Table D45: Further sensitivity analysis results and scenarios: impact on ICER for OTL-200 versus. BSC (Combined Cohort)

Scenario Description	Base Case Values	Lower limit	Upper limit	ICER at lower limit	ICER at upper limit	ICER spread
Discount Rate						
Discount Rate for costs and benefits	Discount Rate: 1.5%	Discount Rate: **0%**	Discount Rate: **3.5%**	[redacted]	[redacted]	[redacted]
Caregiver Disutility						
Number of caregivers required for caregiver disutility	Caregivers Required: GMFC-MLD 2: 0 GMFC-MLD 3: 0 GMFC-MLD 4: 0 GMFC-MLD 5: 2 GMFC-MLD 6: 2	Caregivers Required: GMFC-MLD 2: 0 GMFC-MLD 3: 0 GMFC-MLD 4: 0 GMFC-MLD 5: 2 GMFC-MLD 6: 2	Caregivers Required: GMFC-MLD 2: **0.5** GMFC-MLD 3: **0.5** GMFC-MLD 4: 1 GMFC-MLD 5: 2 GMFC-MLD 6: 2	[redacted]	[redacted]	[redacted]
Time to Engraftment						
Time to engraftment for ES EJ cohort	ES EJ time to engraftment: 6 months	ES EJ time to engraftment: **0 months**	ES EJ time to engraftment: **12 months**	[redacted]	[redacted]	[redacted]

Scenario Description	Base Case Values		Lower limit				Upper limit			ICER at lower limit	ICER at upper limit	ICER spread
Full/Partial Responder Breakdowns												
Full-Responder and Partial-Responders Partial Responders stabilising at GMFC-MLD 1 or 2	Full-Responders: PS LI: [redacted] PS EJ[redacted] Stabilised Partial-Responders: PS LI GMFC 1: [redacted] PS LI GMFC 2: [redacted] PS EJ GMFC 1: [redacted] ES EJ GMFC 1: [redacted] ES EJ GMFC 2: [redacted]		Full-Responders: PS LI: [redacted] PS EJ: [redacted] Stabilised Partial-Responders: PS LI[redacted] PS EJ: [redacted] ES EJ: [redacted]				Full-Responders: PS LI: [redacted] PS EJ: [redacted] Stabilised Partial-Responders: PS LI: N/A PS EJ: N/A ES EJ: [redacted]			[redacted]	[redacted]	[redacted]
Progression Modifiers (PM)*												
Progression modifiers (from GMFC-MLD 0 to GMFC-MLD 6)	PS LI PMs by GMFC-MLD:	PS EJ PMs by GMFC-MLD:	ES EJ PMs by GMFC-MLD:	£73,387 vs BSC	£65,177 vs BSC	£8,209	PS LI PMs by GMFC-MLD:	PS EJ PMs by GMFC-MLD:	ES EJ PMs by GMFC-MLD:	[redacted]	[redacted]	[redacted]

Scenario Description	Base Case Values		Lower limit				Upper limit			ICER at lower limit	ICER at upper limit	ICER spread
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Proportion of Combined MLD Population												
Proportion of disease variant in MLD combined population	Proportion of MLD Population: [redacted]		Proportion of MLD Population: [redacted]				Proportion of MLD Population: [redacted]			[redacted]	[redacted]	[redacted]
Natural history Source Data												
Natural history source data for LI and EJ using Elgun, 2019	Source: OSR-TIGET Natural history Study		Source: **Elgun, 2019 publication**				Source: **Kehrer, 2011 publication**			[redacted]	[redacted]	[redacted]

PS LI, pre-symptomatic Late Infantile; PS EJ, pre-symptomatic Early Juvenile; ES EJ, early-symptomatic Early Juvenile; BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year; PM, progression modifier; SEE, structured expert elicitation; GMFC-MLD, gross motor function classification-MLD; vs. versus

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Figure D11 and Figure D8 below show the results from 10,000 simulations of the incremental cost effectiveness of OTL-200 over BSC at the OTL-200 ex-factory (list) price and patient access scheme (PAS) price.

Figure D9 and Figure D10 below show the Cost Effectiveness Acceptability Curve from 10,000 simulations comparing OTL-200 with BSC at the OTL-200 ex-factory (list) price and at the patient access scheme (PAS) price.

Figure D11: [redacted]

Figure D12: [redacted]

Figure D13: [redacted]

Figure D14: [redacted]

Table D46below shows the maximum and minimum results for costs, life years and QALYs.

These results are discussed in answer to question 12.5.4.

Table D46: Results from 10,000 simulations of OTL-200 and BSC at 1.5% discount rate for costs and benefits (Combined Cohort)

	Max Costs	Min Costs	Max LYs	Min LYs	Max QALYs	Min QALYs	Lower 95% CI of ICER vs BSC	Upper 95% CI of ICER vs BSC
OTL-200 (at List Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200 (at PAS Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC*	£926,013	£669,499	15.21	11.73	1.04	-11.54	N/A	N/A

* Results from the PSA output of the combined cohort of the PAS price of OTL-200 vs BSC

12.5.14 What were the main findings of each of the sensitivity analyses?

OTL-200 versus best supportive care (BSC)

12.5.14.1 One-way sensitivity analysis

All parameter values were varied by +/- 20% or natural limits if these were within the +/- 20% range.

The only variables that impacted on the ICER by [redacted]% or greater in either direction were:

i) The proportion of ES EJ OTL-200 Partial Responders who stabilise at GMFC 2 (upper limit ICER of [redacted]; lower limit ICER of [redacted])

ii) The proportion of PS EJ OTL-200 Full Responders (upper limit ICER of [redacted]; lower limit ICER of [redacted])

iii) The proportion of PS LI OTL-200 Full Responders (upper limit ICER of [redacted]; lower limit ICER of [redacted])

12.5.14.2 Probabilistic sensitivity analysis

The minimum and maximum number of QALYs produced for BSC from the 10,000 simulations for the combined cohort were -11.54 and 1.04; the minimum and maximum total costs were £669,499 and £926,013 (BSC data taken from the output of the PAS price for OTL-200 vs BSC in the combined cohort).

The minimum and maximum number of QALYs produced for OTL-200 from the 10,000 simulations were [redacted] and [redacted]; the minimum and maximum total costs were £[redacted] and £[redacted] at the list price and £[redacted] and £[redacted] at the PAS price.

The minimum and maximum ICERs produced from the simulations were £[redacted] and £[redacted] at the list price and £[redacted] and £[redacted] at the PAS price.

12.5.14.3 Multi-way sensitivity analysis

Further multi-way sensitivity analyses comprising key parameters were conducted. Full results are shown in Section 12.5.12.

- **Discount Rate:** Using the 3.5% discount rate for costs and benefit increases the combined ICER to £[redacted] vs BSC. Reducing the discount rate to 0% decreased the ICER by [redacted]% to £[redacted]
- **Caregiver disutility:** Applying alternative, increased number of caregivers for the caregiver disutility had a minimal impact on the ICER (£[redacted] increase).
- **Time to engraftment:** The use of 0 months for time to engraftment decreased the ICER by [redacted]%, while doubling the value for the time to engraftment to 12 months increased the ICER by [redacted]%.
- **Full/Partial Responder Status:** When the proportion of Full Responders are increased to 100%, the ICER vs BSC decreased by [redacted] %. The use of more conservative percentages of Full Responders increased the ICER substantially.
- **Proportion of Combined MLD Population:** Modifying the combination of MLD combined population to use the minimum recorded proportion of ES EJ patients from the SEE resulted in a [redacted] % decrease in the ICER, while using the maximum recorded proportion of ES EJ patients increased the ICER by [redacted] %.
- **Alternative Natural History Source:** Using the Elgun, 2019 data to inform the natural history MLD progression decreased the ICER by [redacted]%. Whereas the use of Kehrer, 2011 data increased the ICER by [redacted] %.

12.5.15 What are the key drivers of the cost results?

Table D46 shows the percentage of total lifetime costs for each cost category for each of the three interventions. A 1.5% discount rate has been used.

The cost of OTL-200 is the major cost component of total OTL-200 costs followed by the cost of social services and then the cost of drugs.

For BSC the major cost is the cost of social services support followed by the cost of hospitalisations.

Table D47: Percentage of total costs by cost category (Combined Cohort)

Cost Category	Intervention	
	OTL-200	BSC
Product cost	[redacted]	0.00%
Product admin cost	[redacted]	0.00%
Care costs		
Drugs	[redacted]	[redacted]
Medical tests	[redacted]	[redacted]
Medical visits	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]
GP & emergency	[redacted]	[redacted]
Health materials	[redacted]	[redacted]
Social services	[redacted]	[redacted]
Total	**100.00%**	**100.00%**

Abbreviations: BSC=best supportive care; GP=general practitioner. Tables may not sum exactly to 100% due to rounding.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

Not applicable.

12.6 Subgroup analysis

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

A subgroup analysis of each of the eligible MLD disease cohorts were undertaken. Each of the disease cohorts (i.e. PS LI, PS EJ, ES EJ) within the combined cohort are analysed in the subgroup analysis.

12.6.2 Define the characteristics of patients in the subgroup(s).

The populations within the subgroup analysis were as follows:

1. Pre-symptomatic Late Infantile (PS LI): Children with a confirmed diagnosis of Late Infantile MLD without clinical manifestations of the disease,
2. Pre-symptomatic Early Juvenile (PS EJ): Children with a confirmed diagnosis of Early Juvenile MLD without clinical manifestations of the disease
3. Early-symptomatic Early Juvenile (ES EJ): Children with Early Juvenile MLD have early clinical manifestations of the disease, with the ability to walk independently (GMFC-MLD ≤ 1) and before the onset of cognitive decline (IQ ≥ 85).

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Each of the subgroups were aggregated and presented as the combined cohort in the cost-effectiveness model. The subgroup analysis will analyse the each of the underlying disease cohorts that make up the full eligible population in the base case model.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

For the pre-symptomatic Late Infantile (PS LI) variant, the base case incremental cost-effectiveness ratio for OTL-200 versus best supportive care (BSC) is £[redacted] per QALY gained based on the OTL-200 ex-factory (list) price and £[redacted] per QALY gained based on the OTL-200 patient access scheme (PAS) price.

For the pre-symptomatic Early Juvenile (PS EJ) variant, the base case incremental cost-effectiveness ratio indicates that OTL-200 dominates best supportive care (BSC) at [redacted] per QALY gained based on the OTL-200 ex-factory (list) price and [redacted] per QALY gained based on the OTL-200 patient access scheme (PAS) price.

For the early symptomatic, Early Juvenile (ES EJ) variant, the base case incremental cost-effectiveness ratio for OTL-200 versus best supportive care (BSC) is £[redacted] per QALY gained based on the OTL-200 ex-factory (list) price and [redacted] per QALY gained based on the OTL-200 patient access scheme (PAS) price. Total and incremental per patient costs, total and incremental life years gained and total and incremental QALYs gained are presented in Table D47, Table D49 and Table D50. Costs and outcomes (QALYs and life years) are discounted at 1.5%.

Table D48: Base-case results for the Pre-symptomatic Late Infantile (PS LI) variant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
OTL-200 (at ex-factory (list) Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200 (at patient access scheme (PAS) Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	£676,461	9.2	-3.7	N/A	N/A	N/A	N/A

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; BSC, Best supportive care; PAS, Patient access scheme
Costs and benefits discounted at 1.5%.

Table D49: Base-case results for the Pre-symptomatic Early Juvenile (PS EJ) variant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
OTL-200 (at ex-factory (list) Price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200 (at patient access scheme (PAS) Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	£832,097	16.6	-3.6	N/A	N/A	N/A	N/A

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; BSC, Best supportive care; PAS, Patient access scheme

Costs and benefits discounted at 1.5%

Table D50: Base-case results for the Early Symptomatic Early Juvenile (ES EJ) variant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
OTL-200 (at ex-factory (list) Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTL-200 (at patient access scheme (PAS) Price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	£853,005	14.2	-6.4	N/A	N/A	N/A	N/A

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; BSC, Best supportive care; PAS, Patient access scheme
Costs and benefits discounted at 1.5%

Table D51: Undiscounted QALYs from OTL-200 and best supportive care (BSC) and incremental QALYs gained from OTL-200 versus best BSC for the PS LI variant, **Error! Reference source not found.** and Table D52 show

Intervention	**QALYs from intervention**	**Incremental QALYs**
OTL-200	[redacted]	[redacted]
BSC	-4.15	

the undiscounted incremental QALYs for OTL-200 compared with best supportive care (BSC).

Table D51: Undiscounted QALYs from OTL-200 and best supportive care (BSC) and incremental QALYs gained from OTL-200 versus best BSC for the PS LI variant

Intervention	**QALYs from intervention**	**Incremental QALYs**
OTL-200	[redacted]	[redacted]
BSC	-4.15	

Table 51: Undiscounted QALYs from OTL-200 and best supportive care (BSC) and incremental QALYs gained from OTL-200 versus best BSC for the PS EJvariant

Intervention	**QALYs from intervention**	**Incremental QALYs (OTL-200 over comparator)**
OTL-200	[redacted]	[redacted]
BSC	-5.26	

Table D52: Undiscounted QALYs from OTL-200 and best supportive care (BSC) and incremental QALYs gained from OTL-200 versus BSC for the ES EJ variant

Intervention	QALYs from intervention	Incremental QALYs (OTL-200 over comparator)
OTL-200	[redacted]	[redacted]
BSC	-7.7	

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

No. All eligible MLD disease variants have been presented in the submission.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Face validation of the appropriateness of the conceptual model (modelling technique, structure, health states, key sources for model input data, and model outcomes) were judged by multiple clinical experts via clinical expert engagement during model conceptualisation, two economic modelling experts, and via a UK advisory board – see Section 12.2.5 . The structural validity of the model was assessed by multiple clinical experts, two economic modelling experts at individual meetings as well as a UK advisory board. The model utility inputs and underlying case vignettes were validated by key clinical experts in the MLD field and during a UK advisory board. Costs were informed from HCRU values collected from clinical experts during a structured

expert elicitation process. An assessment of the face validity and cross-validation with clinical experts was performed.

Regarding the computerised model, the model, which was parameterised with source data, underwent the following validation:

- Technical verification and evaluation of internal consistency to ensure there are no structural, calculation or programming errors
    - Technical verification was done to check formulas, calculations, links between cells (Microsoft Excel) and syntax (Visual Basic)
    - Comparative assessment of the modelled mortality and disease progression probabilities with the published data as well as with clinical experts consulted during the model conceptualisation process.
    - Extreme value and unit testing comprised setting model transition probabilities to 0 and 1, respectively and turning off specific costs and utility components.
    - Sensitivity analysis of all parameters and extreme value analysis were performed to determine whether model output is as expected to help identify any remaining errors.
    - As a last step, internal consistency was evaluated by comparing the model outputs with source data used for the model development.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

In our SLR of the published economic literature, no health economic models were identified for evaluating potential treatments for MLD.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes, It is considered that the cost-effectiveness analysis presented here is relevant to all groups of patients and specialised services in England that could potentially use OTL-200 as identified in the scope and in accordance with the EMA regulatory indication.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths:

The cost-effectiveness modelling approach used (partitioned survival) was deemed the most appropriate approach to reflect the progressive characteristics of both Late Infantile and Early Juvenile MLD, based on the data available. The model also accounts for the chronic nature of the condition by taking a lifetime perspective. The model framework was conceptualised with leading clinical experts, drawing upon frameworks developed for Duchenne Muscular Dystrophy, and models for similar rare genetic disorders such as CLN2 disease. In an enhancement on these frameworks, this MLD model considered both the motor and cognitive aspects of disease rather than be uni-dimensional,

Whenever possible, OSR-TIGET natural history and clinical trial data were used to inform parameters in the model. Mean values were utilised to better estimate the trajectory and progression of patients with variable durations of follow up in the studies with small sample sizes. Where inputs were unable to be sourced from literature or trial data (e.g. duration of stabilisation, progression modifiers for ES EJ GMFC-MLD specific stages, cognitive distributions by GMFC-MLD stage, etc.), multiple clinical experts were consulted to source these inputs. Multiple rounds of review and validation of inputs were conducted to improve the underlying validity of the clinical expert advice. Results and foundational assumptions were each validated by clinical experts with expertise in MLD disease and experience with OTL-200, in order

to reliably reflect both clinical reality and potentially a changing paradigm with OTL-200 available.

Limitations:

One limitation is that the sample sizes of the clinical studies used to inform the cost-effectiveness model are small, which is typical of trials in populations with ultra-rare paediatric diseases. This uncertainty has been, by providing progression modifiers, which are derived from the partial responder patients within the indicated population. We address the uncertainty associated with small sample size of the OSR-TIGET natural history study, which informs the natural history arm, via deterministic and probabilistic sensitivity analyses based on the standard error around the estimates to determine the certainty of the model results. To assess the generalisability and consistency among alternative sources, we also provided two alternative natural history sources from published literature and assessed the impact of their use on the model results in place of the OSR-TIGET natural history study values.

Another feature of all treatment arms in the cost-effectiveness model is that the follow-up time is relatively short, when compared with the lifetime time horizon of the model. To prevent the model from providing a false sense of precision regarding the patient movements through GMFC-MLD stages, patients are transitioned at time-independent constant rates derived from natural history sources and modified by clinical inputs for OTL-200 patients derived from Orchard Therapeutics clinical trial data. The uncertainty in the progression modifier values of OTL-200 is addressed by providing clinical expert opinion values from the structured expert elicitation in a scenario analysis.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

It is anticipated that the ongoing clinical trials (studies 201222, CUP207394, CUP206258 and HE 205029) will provide longer term data that will validate the assumptions made about the long term efficacy of OTL-200. In addition,

as part of our regulatory commitments, a 15 years post-marketing authorisation long-term follow-up of study (LongTERM-MLD) will be conducted. The aim of this study is to collect efficacy and safety data from patients treated with OTL-200 within the clinical development programme (CDP) or in the post-authorisation setting. Furthermore, information on the epidemiology as well as the disease variant and symptomatic status of patients at point of treatment will be available in the future. Therefore the robustness of the cost-effectiveness analyses could be enhanced with the data that become available from these sources.

In a paradigm where OTL-200 is available in the UK, the need for newborn screening will become paramount as pre-symptomatic treatment with OTL-200 is associated with improved clinical outcomes. Given this, it is anticipated that the introduction of newborn screening will lead to an increase in the proportion of pre-symptomatically diagnosed MLD patients and a reduction in the proportion of symptomatically diagnosed patients. A further analysis could be conducted to assess the impact of OTL-200 on a future paradigm where newborn screening for MLD is conducted to determine OTL-200's cost-effectiveness. OTL-200 is more cost-effective in pre-symptomatically treated patients, and it would be expected that the cost-effectiveness would be improved in this scenario

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

As discussed in Section 6.2, the estimated prevalence of MLD in the UK is 0.04 per 100,000. However it is expected that the number of patients eligible for OTL-200 treatment will be lower than this as only pre-symptomatic LI and pre-and early-symptomatic EJ patients are in line with the marketing authorization for OTL-200. At the NICE scoping workshop held on the 27th January 2020, clinical experts estimated that [redacted] LI patients and [redacted] Juvenile patient would be eligible for OTL-200 treatment given the proposed indication. Therefore it is anticipated that every year [redacted] patients would be eligible for treatment with OTL-200.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

The expected uptake of OTL-200 is presented in Table D53 below. As there are currently no treatments specifically indicated for MLD disease, it is assumed that all eligible patients would take up treatment for OTL-200 following a positive NICE recommendation. In the 1st year, it is assumed only [redacted] patient would uptake treatment based on anticipated NICE recommendation in the 2nd half of the year. This would rise to [redacted] patients in the 2nd and 3rd year. Finally due to the impact of some of the early diagnosis initiatives the company is embarking on, in the future it is expected that more MLD patients will be diagnosed at the pre-symptomatic or early -symptomatic stage, hence the increase in number of patients in Year 4 compared to Year [redacted].

Table D53: Eligible patients for OTL-200 over 5 years in England

	Year 1	Year 2	Year 3	Year 4	Year 5
Total patients treated with OTL-200-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PS LI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PS EJ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ES EJ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc.).

In addition to technology costs, other costs associated with the introduction of OTL-200, and considered in the budget impact analysis, are: (i) Administration costs; and (ii) Monitoring costs

13.4 Describe any estimates of resource savings associated with the use of the technology.

By delaying disease progression, OTL-200 maintains patients in earlier health states for longer than the standard of care — see Section 12 for more details. Later health states in the cost-effectiveness model are associated with greater resource use, such as greater numbers of appointments with specialist clinicians, nurses and therapists. Other costs, such as increased hospital stays, and social care costs. As such, resource savings can be expected due to the greater number of patients remaining in less severe health states compared to if patients were receiving standard of care.

As noted above, it is also anticipated that overtime newborn screening for MLD would be established in England leading to an increase in the diagnosis of patients in the pre-symptomatic stage. The earlier diagnosis of patients in the disease pathway will increase the cost savings associated with delayed

disease progression by enabling patients to remain in less severe health states.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It is not anticipated that any additional resource savings or redirection of resources would occur.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

In terms of additional savings, the earlier health states of the disease are associated with a lower requirement of care. By delaying progression into the later health states, and increasing the time spent in the earlier health states, the level of care required for patients is lower, and lower productivity losses can be expected as a result.

Due to the rarity of the disease and nature of technology, there would be very limited specialist centres able to administer treatment. As a result, there can be substantial journey times and transportation costs for the family of the patient.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Base-case estimates of the budget impact associated with the introduction of OTL-200 are presented in Table D54 and Table D55, assuming each of the proposed PAS price and the list price, respectively

Table D54: Budget impact of OTL-200 in England over 5 years (proposed PAS price)

Costs	Year				
	1	2	3	4	5
Total costs in scenario without OTL-200	£134,182	£257,745	£257,745	£370,830	£370,830
Total costs in scenario with OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table D55: Budget impact of OTL-200 in England over 5 years (List price)

Costs	Year				
	1	2	3	4	5
Total costs in scenario without OTL-200	£134,182	£257,745	£257,745	£370,830	£370,830
Total costs in scenario with OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The NHS has a single budget for specialised services of approximately £16.6 billion,101 which includes medicines. The budget impact of OTL-200 in year 1 represents approximately [redacted] % of this.

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc.).

The key limitation of the budget impact analysis is uncertainty around the estimates of patient numbers. In addition, the budget impact analysis uses annual healthcare resource use costs generated by the cost-effectiveness model and so is associated with the same limitations for:

- The proportion of patients in the various disease subgroups (PS LI, PS EJ and ES EJ); and
- The calculation of cost inputs.

However, the key driver of cost per patient is the acquisition cost of OTL-200 (see Section 12.5.8), which is a known parameter.

Section E — Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

Summary:

- OTL-200 will have a significant impact on the NHS, other government bodies, and caregivers and their families by enabling the affected children to grow up and lead normal lives.
- UK caregivers dedicate the vast majority of their time caring for their child with MLD (15 hours per day), including time spent in and out of the healthcare system (21 outpatient visits and 12 days spent in the hospital per year), throughout the child and their family's journey with MLD. (Pang et al., 2020)
- The financial burden of MLD is driven by adaptations, extra nursing assistance and loss of work as a result of caring for their child, which has been estimated to cost up to £260,000 over a 12-months period.
- OTL-200 would be administered in a very small number (1–2) of specialised centres, which would enable these centres to gain significant

additional experience in using and establishing the infrastructure to deliver ex vivo gene therapies.

- Clinical trial patients and those treated in the post-market authorisation setting will be asked to enrol in a follow up study for up to 15 years (LongTERM-MLD) to better understand the long-term effects of OTL-200.

14 Impact of the technology beyond direct health benefits

The evidence to support the claims outlined in Sections 13.1–13.5 is based on a MLD caregiver study (Pang et al., 2020) that was designed to comprehensively qualitatively and quantitatively assess the burden of MLD based on a survey of 21 caregivers across a range of domains, including personal and family relationships, personal time, daily activities, physical and mental health, social life, leisure activities, work productivity, and finances. The study was based on a moderator guided survey and follow-up extended semi-structured telephone interviews with caregivers from the UK (n=6), Germany (7) and the US (n=8). The questionnaires were extensively validated with clinical KOLs and representatives of patient organisations and submitted for IRB approval (Pang et al., 2020). Careful consideration was given to the study design due to the challenges in recruitment because of MLD as an ultra-rare disease and the methodological issues associated with proxy administration (which are not limited to this particular study). The MLD caregiver study took over 20 months from design, validation, IRB approval, recruitment through to analysis.

Similar findings were reported in personal communications with three patient advisory groups (MPS Society, the MLD Support Association UK and the ArchAngel MLD Trust) to increase understanding of the natural history of MLD, its impact and burden on patients and their families.

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

As with other chronic conditions, the impact of MLD on caregivers/family is greatly underestimated. The burden of caring for patients with MLD is largely attributed to the appropriate management of the patient's daily life. For patients with MLD, most become wheelchair dependent or severely immobile and patients never achieve social independence. MLD patients are consequently highly reliant on third-party assistance with cognitive impairment, reduced self-care and reduced locomotive abilities as the key reasons behind this dependency.

Substantial proportion of the costs incurred outside of the NHS and personal social services

The caregiver study (Pang et al., 2020) found that the greatest financial strain for caregivers and families comes from out-of-pocket expenses (e.g. home modification, transportation), waiting for funding, missed work and/or having to stop work to care for their child, while potentially having to hire additional care support (see Section 13.3 for more information).

Significant benefits other than health

As demonstrated in the overview of clinical studies presented in Section C, children treated with OTL-200 are anticipated to show normal development of motor function and cognitive skills, sustaining the time during which they are comfortable and alert and allowing them to develop and maintain daily activities of living. These qualitative outcomes are consistent with the totality of evidence of long-term clinical benefit.

These findings are further supported by the caregiver studies (Pang et al., 2020 and PAG draft report, 2020) that have reported that OTL-200 will reduce

the burden on caregivers and their families and therefore impacting several key factors including:

- The emotional and psychological well-being of caregivers and their families
- The ability to build normal relationships with family, friends and social relationships
- The education and social interaction of the affected child who has a chance to grow up and lead normal lives
- Work productivity gains for parents/caregivers and ability to pursue career ambitions
- Family finances and outside sources of financial support, including friends

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Costs to government bodies

The high degree of patient burden driven by the rapid simultaneous decline in cognitive and physical functions means that parents are usually the main provider of care, with one parent often becoming a full-time caregiver, providing round-the-clock care. Based on the MLD caregiver study (Pang et al., 2020) UK caregivers (n=6) spend on average 15 hours per day caring for their child and undertake 21 outpatient visits and 12 days in hospital per year. On average for each affected child, 3 caregivers (parents and nurse assistant) made up the care team. Others drafted into the care team included grandparents, siblings, uncles and aunts. Half of the caregivers (n=11) received on average over the past year 6 hours per day of nursing care. Due to the round the clock care required a caregiver indicated even going grocery shopping was a difficult undertaking.

In addition, children with MLD will require extra education/special schooling and are unlikely to ever obtain full-time employment. In the MLD caregiver survey, 25% of children were not attending school or receiving home

schooling. Of those attending school, over 50% often or almost always experienced problems, especially keeping up with activities, forgetting things, and paying attention in class as measured by the school functioning domain of the PedsQL. (Pang et al., 2020)

This means that families with a child affected by MLD receive financial assistance, such as child tax benefits, disability allowance, carer allowance and income support. These expenditures need to be covered by the Department of Work and Pensions, Department for Education, the Department of Health and Social, the Department of Communities and Local Government and Local County Councils.

Cost savings to government bodies

Children treated with OTL-200 are anticipated to show normal development of motor function and cognitive skills, sustaining the time during which they are comfortable and alert and allowing them to develop and maintain daily activities of living, such as walking and self-feeding, as well as build normal relationships with family members and caregivers. This step-change in the management of MLD will children to attend a normal school, receive an education and a chance to grow up and lead normal lives.

In addition to providing direct clinical benefits to the patient, OTL-200 is anticipated to have a significant impact on the daily lives of the family and caregivers by improving quality of life, wellbeing and reducing time spent caring. A reduction in the length and intensity of caring may also reduce the risk of mental health problems and familial dynamics and allowing the caregivers/parents to return to work and the ability to pursue career ambitions.

These findings are further supported in personal communications with three patient advisory groups (MPS Society, the MLD Support Association UK and the ArchAngel MLD Trust) that reported that most children treated with OTL-200 are attending mainstream schools, that time spent in the healthcare system has significantly decreased and that caregivers are able to return to work and pursue their career ambitions.

Therefore, OTL-200 is expected to reduce the current expenditure by government, including the Department of Work and Pensions, Department for

Education, the Department of Health and Social, the Department of Communities and Local Government and Local County Councils.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Caregivers and families are faced with many emotional, professional, organisational and financial challenges that are not covered by the NHS. Given the rapid disease progression, families have to quickly adapt to the reality of caring for their affected child, which also comes with a tremendous impact on the family's financial situation (Pang et al., 2020). Therefore, the urgency of need is often not compatible with NHS processing timelines or is outside the standard NHS eligibility criteria. In addition, the specialist nature of the need and lack of local funding further adds to the financial burden for families.

Families can receive financial assistance for certain elements of care, such as financial aid for wheelchairs and home adaptations; however, home adaptations are means-tested, therefore not all families will receive support. While 57% of respondents (n=21) in the MLD caregiver study (Pang et al., 2020) had to depend on external sources of funding to help with management of the patient's disease, the caregivers from the UK (n=6) reported that 84% of the national annual median income per capita is consumed by out-of-pocket expenses and forgone income. (Pang et al., 2019)

The most significant costs covered by the families include home modification, transportation, and loss of income:

- The cost of adaptations to the home and appliances and other care equipment are notable drivers of cost for caregivers
    - Families are required to modify their home to be able to care for their affected child. A patient advisory group highlighted in a personal communication that the major items funded through the families include home modifications at an average cost of £30,000 (in excess of social services grant), specialist care (up to £13,200 per year) and other items such as specialist

wheelchair/car seat, shaky vest (for secretions) that can add up to more than £16,000.

    - One family estimated that caring for a child with LI MLD over a 12-month period has cost them more than £260,000 to cover purchasing of essential home equipment, community services, lost earnings and respite costs. In addition, the family "expects on average (excluding adaptations and equipment already provided) a further £200,000 cost burden per year."

- The cost of transportation and the amount of time needed to travel to and from hospitals to access specialised services and care and overnight accommodation/meals

    - Due to the rarity and severity of MLD, there are only a few centres in the UK with the specialist expertise needed to care for these patients. Therefore, caregivers have reported that they spend on average of 1.3 hours for each round trip to the specialist centres. Caregivers also spend on average 12 days in the hospital and make 21 outpatient visits per year. (Pang et al., 2020)

    - Similar findings were reported in personal communications with a patient group that has reported accommodation costs for family receiving treatment away from home can cost up to £6,000.

- Loss of income

    - In the MLD caregiver study (Pang et al., 2020), caregivers (n=21) described the financial impact of caring for a child with MLD disease, which included giving up work to care or being unable to return to work, having time off from work, additional expenses, benefits and waiting for funding. 83% of the caregivers were forced to miss work with an average of 68% of the time being unpaid; 65% experienced loss of income due to stopping work or moving to part-time. (Pang et al., 2020)

- Similarly, in the caregiver study (Harrington et al., 2016) findings were reported that caregivers experience financial strain because of their child's illness (13/16; 81%), and half (8/16; 50%) reported being unable to work because of caregiving responsibilities.

The costs incurred by families and government bodies (Section 13.2) have not been included in the cost-effectiveness and budget impact model, since it is not possible to provide estimates at this time. Therefore, the presented cost-effectiveness and budget impact figures for OTL-200 in Section D are conservative estimates.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

Parents are usually the main provider of care, with one parent often becoming a full-time caregiver, providing round-the-clock care. Due to the amount of effort required to care for a patient with MLD, there is also potential for sibling abandonment, which may impact on the development of the unaffected sibling. In the MLD caregiver study, UK caregivers (n=6) reported that they spend on average 15 hours per day caring for their child, this included (Pang et al., 2020):

- General health maintenance (e.g. bathing, brushing team, changing nappies, emptying catheter)
- Moving or lifting (e.g. in/out of bed, bathroom, vehicle)
- Monitoring and checking vitals (e.g. blood pressure, temperature, oxygen)
- Feeding (with or without tube)
- Medication administration (at multi-hour intervals, sometimes administered in the middle of the night)
- Organising therapies (e.g. physical, occupational, speech, music). I

On average for each affected child, 3 caregivers (parents and nurse assistant) made up the care team. Others drafted into the care team included grandparents, siblings, uncles and aunts.

In addition, the rapid initial decline in health as well as moments of crisis associated with MLD leads to significant time spent in and out of the healthcare system with on average 21 outpatient visits and 12 days spent in the hospital per year throughout the child and their family's journey with MLD. (Pang et al., 2020)

Therefore, caregivers often find themselves making sacrifices in social and leisurely activities as well as overall lifestyle changes to accommodate level of care required. The MLD caregiver study (Pang et al. 2020) found that 95% of caregivers (n=21) had to make significant lifestyle changes and 71% indicated that they missed leisure activities they once enjoyed. This can have emotional impact stemming from loss of identity, poor self-care, feeling unable to help their child, which can lead to anxiety and depression, and some shifts in family dynamics including spousal conflicts. (Pang et al., 2020)

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Ongoing Study 205756 has enrolled six patients (at the last data cut) to assess safety and efficacy of treatment using the cryopreserved formulation of OTL-200, with an estimated primary completion date in Q3 2022.

In addition, in line with regulatory requirements, a 15 years post-marketing authorisation long-term follow-up of study (LongTERM-MLD) will be conducted. The aim of this study is to collect efficacy and safety data from patients treated with OTL-200 within the clinical development programme (CDP) or in the post-authorisation setting.

There are a number of initiatives ongoing in the UK with respect to new-born screening (NBS) in metabolic disorders and MLD specifically. Orchard Therapeutics is collaborating with the UK Metabolic Disorder Screening

Laboratories and also relevant Patient Organisations to initiate a UK based MLD dried blood spot NBS methodology validation study which if successful could lead onto a full UK Pilot MLD NBS Trial; as well as a multi-stakeholder platform to raise awareness in both the wider healthcare and political arenas of the need for MLD and other metabolic disorders where an effective treatment is available that also fulfil the Wilson and Jungner Criteria used by the UK NSC.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Orchard Therapeutics was founded in the UK in 2015 as a small, start-up London-based biotechnology company, dedicated to bringing transformative gene therapies to patients with serious and life-threatening rare diseases. It was spun-out of collaboration with several clinical centres of excellence including Great Ormand Street Hospital and UCL Business (the technology transfer company of University College, London (UCL) and works closely with other organisations within the UK biotechnology eco-system such as Oxford BioMedica, Cell and Gene Therapy Catapult and BIA. With global headquarters in London, Orchard Therapeutics is a leading biotechnology employer of UK-based talent and with ongoing clinical trials and research throughout the UK, Orchard Therapeutics remains highly committed to securing the best possible care for UK patients and adding to the positive progression of science and research in England and beyond to support the translation of research to real medical innovation that can improve outcomes for patients.

OTL-200 is an ex vivo genetically modified autologous $CD34^+$ haematopoietic stem and progenitor cell gene therapy administered as a dispersion for infusion. It is the first treatment option (pharmacological or otherwise) that addresses the underlying biological cause of this severe, rapidly progressing and life-limiting disease.

As such, OTL-200 is expected to restore ARSA enzyme activity in the brain, addressing the underlying cause of the disease and reducing the progressive,

pathologic accumulation of lysosomal storage material in the brain and body so as to stabilise or slow the rapid and predictable decline in motor and cognitive function described in Section 6.1. Therefore, this transformative therapy will provide a highly durable effect, allowing children to develop normal cognitive and motor skills whilst ensuring value and sustainability for healthcare systems and society.

OTL-200 would be administered in a very small number (1–2) of specialised centres, which would enable these centres to gain significant additional experience in using and establishing the infrastructure to deliver ex vivo gene therapies particularly for neurological conditions which could then be applied for future treatments for other diseases and conditions. It may also provide the specialised centres the opportunity to treat patients from other countries, adding to the reputation of these centres.

The increased shelf-life of the cryopreserved formulation is an innovation that also confers the possibility of expanded geographic supply of OTL-200 to selected clinical centres which are distant from the drug product manufacturing site and in most cases closer to the patients' and families' home.

As this is the first *ex vivo* gene therapy for a neurological condition, UK clinicians have suggested that this paves the way for the future treatment of other neurological and non-neurological conditions where no adequate treatments exist due to the blood brain barrier preventing drugs from being able to reach the brain.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

As described in Section 14.5, all patients previously treated within the CDP (after a minimum of three years follow-up in their respective study/programme) and treated in the post-authorisation setting will be invited to consent to participate in the LongTERM-MLD study. The objective of this study is to evaluate durability of clinical efficacy, survival and safety following

treatment with OTL-200, at multiple timepoints up to 15 years post-treatment. This study also aims to gather specific efficacy and safety data in ES/EJ MLD patients. It is anticipated that [redacted] patients will participate in the study.

In addition, to the data collected in the LongTERM-MLD study, longer term data will also be available from the ongoing clinical trials 201222 and the phase III study, as well as the EAPs.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

For the LongTERM-MLD study Periodic Benefit-Risk Evaluation Reports (PBRERs) and annual status updates will be generated as/when required per regulatory requirements. In addition, formal interim analyses will be triggered at various timepoints. The interim analysis will review engraftment, efficacy and safety data, which will also include data from patients in the CDP. Efficacy data will be compared with natural history data from patients of the same disease variant, matched for age. These analyses will also include subgroup analyses for pre-symptomatic and early symptomatic patients, and commercial cryopreserved drug product (DP) versus fresh formulation DP.

Full statistical methods for safety and efficacy analyses, procedures for accounting for missing data and definition of analysis populations will be detailed in the statistical analysis plan(s) (SAPs).

In case that a positive NICE recommendation is made conditional on a Managed Access Agreement (MAA), then Orchard Therapeutics will work with the key stakeholders in developing a data collection and monitoring plan which will then form the basis for the re-evaluation of OTL-200 following the MAA period.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The SmPC stipulates that OTL-200 must be administered in a qualified treatment centre with experience in HSCT in other diseases. (Libmeldy SmPC, 2020)

The infrastructure and expertise to proceed with autologous transplantation is already in existence through NHS apheresis service and transplant centres. Orchard Therapeutics is committed to investing time and resources to support and upskill the relevant cross-functional teams within the treatment centres. No other additional facilities, technologies or infrastructure will be required.

The expertise to proceed with autologous transplantation is already in existence through NHS apheresis service and transplant centres.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

It is not anticipated that changes to the current NHS service will be required, since OTL-200 must be administered in a qualified treatment centre with experience in HSCT in other diseases and the eligible patient population is extremely small at approximately [redacted] per year. (Libmeldy SmPC, 2020)

The Orchard Therapeutics process for the choice and qualification of OTL-200 Treatment Centres is based on the centres fulfilling objective clinical, regulatory and logistical criteria (see Appendix E for more details).

15 Appendices

Appendix A

Table A1. GLIA guidance on the preventive and symptomatic care of patients with leukodystrophies

Topic	Details
Musculoskeletal issues	
Spasticity	• Baclofen or diazepam in combination with physical therapy and daily stretching routines • Chemodenervation with botulinum toxin or intramuscular neural lysis with phenol • More invasive treatments such as intrathecal baclofen, Surgical interventions to lengthen or sever tendons or nerve pathways
Dystonia	• Trihexyphenidyl (Artane) • Dopaminergic drugs, such as Levodopa, and tetrabenazine • Oral baclofen and benzodiazepines • More invasive treatments include intrathecal baclofen and, in rare cases, deep brain stimulation (DBS)
Low bone mass/density and fractures	• Active monitoring of bone health and vitamin D levels (25-OH-D) • Consultation with a bone specialist or endocrinologist
Hip dislocation	• Physiatry and orthopaedics to discuss appropriate management options • Surgery • Adductor releases and tone management, in patients under five years of age. • Reconstructive surgery, in patients after six years of age
Scoliosis	• Braces and external frames • Spinal orthoses • Spinal surgery if the curve exceeds a Cobb angle of 40–50°
Ambulation	• Age-appropriate devices (e.g. orthotics, braces, gait trainers, walkers, lifts, and standers). • Outpatient physical therapy

Nutrition, bowel and urinary tract	
Hypersalivation	• Oromotor or behavioural exercises, positioning, replacing medications that stimulate saliva secretion • Optimization of constipation, scoliosis, and gastroesophageal reflux • Anticholinergics, which include hyoscine (oral/transdermal Scopolamine) and trihexyphenidyl (Artane) • Sublingual 1% atropine ophthalmic solution • Glycopyrrolate (in children older than 3 years of age). • More intense or invasive treatments (targeted botulinum toxin A injections and salivary gland surgery
Upper gastrointestinal complications	• Nutritionally complete diet, consulted by dietician • Proper positioning, adjustment of food consistency, pacing of feeding, and equipment • An expedited consultation with gastroenterology or general surgery for consideration of gastrostomy (G-tube) or jejunostomy (J-tube) tube placement
Gastroesophageal reflux	• Optimise position and food consistency during feeding • Adjunctive medications, such as acid buffering agents, antisecretory agents, and prokinetic • Ranitidine, lansoprazole, and omeprazole • Surgical interventions such as nissen fundoplication is often offered in conjunction with a gastrostomy or gastrojejunal tube placement
Bladder health	• Prophylactic anti-microbial agents • With bladder retention, urinary catheterisation as guided by urology
Gastrointestinal and urinary health	• Laparoscopic cholecystectomy for polyps larger than 5 mm

Respiratory health, sleep and communication	
Progressive respiratory insufficiency	• Infection prevention • Key airway maintenance strategies • Mechanical ventilation
Communication	• A comprehensive augmentative and alternative communication (AAC) evaluation
Sleep	• Optimisation of sleep hygiene, with a consistent sleep schedule, avoiding screen time 1–2 h prior to bedtime, and minimising unnecessary medical interventions at night • Primary caregivers can record a sleep diary • Off-label options include clonidine, tricyclic antidepressants, and benzodiazepines • Melatonin is often used to help with sleep initiation
Neurologic issues	
Pain	• Gabapentin • Benzodiazepines and neuroleptics
Seizures	• Rectal diazepam and buccal or intranasal midazolam
Autonomic nervous system dysfunction	• Gabapentin, cyproheptadine, baclofen, beta-blockers, and clonidine • For acute attacks, diphenhydramine, acetaminophen, or ibuprofen
Additional neurologic consideration	• Gabapentin, start at 15–20 mg/kg/d divided 2–3 times daily and to escalate as needed to 60 mg/kg/d. • Non-validated alternatives include pregabalin, topiramate, tricyclic antidepressants, and valproic acid • In refractory cases, benzodiazepines can be used with caution • Risperidone and valproic acid may be helpful mood and behaviour stabilisers

Endocrine guidelines	
Other leukodystrophy-specific endocrine issues	• Hormone replacement therapy administered as needed
Post-transplantation endocrine considerations	• Increased risk for endocrinopathy secondary to medication, irradiation, and the transplant itself • Post-transplant osteoporosis should also be assessed and treated as clinically indicated
Additional system-specific concerns	
Autoimmune disorders	• Annual testing of TSH levels, as well as clinical screening for other autoimmune diseases
Cardiac issues	• If suspected, prompt referral to a cardiologist is recommended
Opthalmologic issues	• Where appropriate, ocular lubricants should be used
Dental guidelines	• A specialist in paediatric special-needs dentistry can be useful
Coordination of care	
Biopsychosocial assessment	• Clinical team of physicians and social workers should discuss goals of care regularly with the family
Clinical care plan	• The plan should include a list with each provider and their specific recommendations for follow up visits, studies, and medications and 'red flags' to facilitate communication. • Patients/families to independently keep track of their local care team visits, medication changes, lab results, and medical treatments
Transitions in care	• Conversations on transitions of care should be started early to familiarize the family with evolving needs.
Strengthening family supports	• Online resources are able to quickly report on relevant innovations, changes in care strategies and resources, to communicate about research and therapeutic opportunities, and allow a more active role as parents, clients, and patient advocates

Appendix B

15.1 Appendix B1: Search strategy for clinical evidence

15.1.1 The specific databases searched and the service provider used

The following databases were searched:

- MEDLINE and MEDLINE In-Process Citations (Ovid)
- Medline Daily Update, and Epub Ahead of Print (Ovid)
- PubMed (NLM)
- Embase (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Social Science Citation Index (SSCI) (Web of Science)
- NHS EED (CRD)
- EconLit (EBSCO)
- Clinicaltrials.gov
- WHO ICTRP (Unable to search on 19/5/2020)
- Orphanet Clinical Trials (internet)
- WORLDSymposium (internet)
- Northern Light Life Sciences Conference Abstracts (Ovid)

15.1.2 The date on which the search was conducted.

Searches were conducted from the 12th May 2020 to 4th June 2020. Dates for each database are listed below:

- MEDLINE and MEDLINE In-Process Citations: 19/05/2020
- Medline Daily Update, and Epub Ahead of Print: 12/05/2020
- PubMed: 13/05/2020
- Embase: 12/05/2020
- Cochrane Central Register of Controlled Trials (CENTRAL): Issue 5, May 2020, searched 13/05/2020
- Social Science Citation Index (SSCI): 14/05/2020
- NHS EED: 14/05/2020

- EconLit: 14/05/2020
- Clinicaltrials.gov: 19/05/2020
- WHO ICTRP: Unable to search on 19/05/2020
- Orphanet Clinical Trials: 02/06/2020
- WORLDSymposium: 04/06/2020
- Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2020/week18

15.1.3 The date span of the search.

- MEDLINE and MEDLINE In-Process Citations (Ovid): 1946-18/05/2020
- Medline Daily Update, and Epub Ahead of Print (Ovid): up to 11/05/2020
- PubMed (NLM): up to 13/05/2020
- Embase (Ovid): 1974-11/05/2020
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to Issue 5, May 2020
- Social Science Citation Index (SSCI) (Web of Science): 1988-07/05/2020
- NHS EED: up to 31/03/2015
- EconLit: 1886-07/05/2020
- Clinicaltrials.gov: up to 19/05/2020
- WHO ICTRP: Unable to search on 19/05/2020
- Orphanet Clinical Trials: up to 02/06/2020
- WORLDSymposium: 2018-04/06/2020
- Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2020/week18

15.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline & In-Process Citations (Ovid): 1946-18/05/2020, searched 19/05/2020

Number	Search terms	Number of results

1	Leukodystrophy, Metachromatic/	1223
2	(MLD and (gene$ or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph$ or leucodystroph$)).ti,ab,ot.	853
3	(Metachromatic adj2 (leukoencephal$ or leucoencephal$ or leukodystroph$ or leucodystroph$)).ti,ab,ot,kw,kf,hw.	1665
4	(("Arylsulfatase A" or "arylsulphatase A" or "epididymis secretory sperm binding protein") adj2 deficien$).ti,ab,ot,kw,kf,hw.	233
5	Greenfield$ Disease.ti,ab,ot,kw,kf,hw.	6
6	(Cerebroside adj2 (Sulfatase or Sulphatase) adj2 Deficien$).ti,ab,ot,kw,kf,hw.	7
7	(cerebroside adj2 (sulfate or sulphate) adj2 storage disease).ti,ab,ot,kw,kf,hw.	0
8	((ASA or ESSPB or ARSA) adj2 Deficien$).ti,ab,ot,kw,kf,hw.	125
9	Cerebroside Deficien$.ti,ab,ot,kw,kf,hw.	0
10	((diffuse or metachromatic) adj3 (Cerebral or brain) adj3 sclerosis).ti,ab,ot,kw,kf,hw.	2362
11	((sulfatide or sulphatide) adj2 lipidosis).ti,ab,ot,kw,kf,hw.	18
12	(mckusick-25010 or mckusick25010).ti,ab,ot,kw,kf,hw.	0
13	(sulfatidosis or sulphatidosis).ti,ab,ot,kw,kf.	18
14	or/1-13	4270
15	animals/ not (animals/ and humans/)	4663669
16	**14 not 15**	**4000**

Medline Daily Update & ePubs Ahead-of-Print (Ovid): up to 11/05/2020, searched 12/05/2020

Number	Search terms	Number of results
1	Leukodystrophy, Metachromatic/	0
2	(MLD and (gene$ or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph$ or leucodystroph$)).ti,ab,ot.	15
3	(Metachromatic adj2 (leukoencephal$ or leucoencephal$ or leukodystroph$ or leucodystroph$)).ti,ab,ot,kw,kf,hw.	4
4	(("Arylsulfatase A" or "arylsulphatase A" or "epididymis secretory sperm binding protein") adj2 deficien$).ti,ab,ot,kw,kf,hw.	2
5	Greenfield$ Disease.ti,ab,ot,kw,kf,hw.	0
6	(Cerebroside adj2 (Sulfatase or Sulphatase) adj2 Deficien$).ti,ab,ot,kw,kf,hw.	0
7	(cerebroside adj2 (sulfate or sulphate) adj2 storage disease).ti,ab,ot,kw,kf,hw.	0
8	((ASA or ESSPB or ARSA) adj2 Deficien$).ti,ab,ot,kw,kf,hw.	2
9	Cerebroside Deficien$.ti,ab,ot,kw,kf,hw.	0
10	((diffuse or metachromatic) adj3 (Cerebral or brain) adj3 sclerosis).ti,ab,ot,kw,kf,hw.	0
11	((sulfatide or sulphatide) adj2 lipidosis).ti,ab,ot,kw,kf,hw.	0
12	(mckusick-25010 or mckusick25010).ti,ab,ot,kw,kf,hw.	0
13	(sulfatidosis or sulphatidosis).ti,ab,ot,kw,kf.	0
14	or/1-13	17
15	animals/ not (animals/ and humans/)	2217
16	**14 not 15**	**17**

PubMed (NLM) (Internet): up to 13/05/2020, searched 13/05/2020

Number	Search terms	Number of results
19	**Search (#17 AND #18)**	**55**
18	Search (((pubstatusaheadofprint[sb] OR publisher[sb] OR pubmednotmedline[sb])))	3656056
17	Search (#13 NOT #16)	1709
16	Search (#14 NOT (#14 AND #15))	3325716
15	Search human*[tiab]	2727458
14	Search ((rat[tiab] or rats[tiab] or mouse[tiab] or mice[tiab] or murine[tiab] or rodent[tiab] or rodents[tiab] or hamster[tiab] or hamsters[tiab] or pig[tiab] or pigs[tiab] or porcine[tiab] or rabbit[tiab] or rabbits[tiab] or animal[tiab] or animals[tiab] or dogs[tiab] or dog[tiab] or cats[tiab] or cow[tiab] or bovine[tiab] or sheep[tiab] or ovine[tiab] or monkey[tiab] or monkeys[tiab]))	4131203
13	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #10 OR #11 OR #12)	1840
12	Search (((((“sulfatide lipidosis”[Title/Abstract]) OR “sulphatide lipidosis”[Title/Abstract]) OR “mckusick-25010”[Title/Abstract]) OR “mckusick25010”[Title/Abstract]) OR sulfatidosis[Title/Abstract]) OR sulphatidosis[Title/Abstract]	36
11	Search (((“diffuse Cerebral sclerosis”[Title/Abstract]) OR “metachromatic Cerebral sclerosis”[Title/Abstract]) OR “diffuse brain sclerosis”[Title/Abstract]) OR “metachromatic brain sclerosis”[Title/Abstract]	40
10	Search (((((“epididymis secretory sperm binding protein deficiencies”[Title/Abstract]) OR “epididymis secretory sperm binding protein deficienct”[Title/Abstract]) OR “Cerebroside Deficiency”[Title/Abstract]) OR “Cerebroside Deficiencies”[Title/Abstract]) OR “Cerebroside Deficient”[Title/Abstract])	0
8	Search (((((“ESSBP Deficiency”[Title/Abstract]) OR “ESSBP Deficiencies”[Title/Abstract]) OR “ESSBP Deficient”[Title/Abstract]) OR “epididymis secretory sperm binding protein deficiency”[Title/Abstract]) OR “epididymis secretory sperm binding protein deficiencies”[Title/Abstract]) OR “epididymis secretory sperm binding protein deficient”[Title/Abstract]	0
7	Search (((((((“Cerebroside Sulphatase storage disease”[Title/Abstract]) OR “cerebroside Sulfatase storage disease”[Title/Abstract]) OR “ARSA Deficiency”[Title/Abstract]) OR “ARSA Deficiencies”[Title/Abstract]) OR “ARSA Deficient”[Title/Abstract]) OR “ASA Deficiency”[Title/Abstract]) OR “ASA Deficiencies”[Title/Abstract]) OR “ASA Deficienct”[Title/Abstract]	61
6	Search (“Cerebroside Sulfatase Deficiency”[Title/Abstract]) OR “Cerebroside Sulphatase Deficiency”[Title/Abstract]	1
5	Search (“Arylsulfatase A Deficiency”[Title/Abstract]) OR “Arylsulphatase A Deficiency”[Title/Abstract]	62
4	Search (“Greenfield Disease[Title/Abstract]) OR “Greenfields Disease[Title/Abstract]	0
3	Search (((“Metachromatic leukoencephalopathy”[Title/Abstract]) OR “Metachromatic leucoencephalopathy”[Title/Abstract]) OR “Metachromatic leukodystrophy”[Title/Abstract]) OR “Metachromatic leucodystrophy”[Title/Abstract]	1324
2	Search ((MLD[Title/Abstract]) AND (gene*[Title/Abstract] OR ARSA[Title/Abstract] OR ASA[Title/Abstract] OR arylsulfatase[Title/Abstract] OR arylsulphatase[Title/Abstract] OR leukodystroph*[Title/Abstract] OR leucodystroph*[Title/Abstract]))	563
1	Search “Leukodystrophy, Metachromatic”[Mesh:NoExp]	1223

Embase (Ovid): 1974-11/05/2020, searched 12/05/2020

Number	Search terms	Number of results
1	Leukodystrophy, Metachromatic/	1223
2	(MLD and (gene$ or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph$ or leucodystroph$)).ti,ab,ot.	850
3	(Metachromatic adj2 (leukoencephal$ or leucoencephal$ or leukodystroph$ or leucodystroph$)).ti,ab,ot,kw,kf,hw.	1665
4	(("Arylsulfatase A" or "arylsulphatase A" or "epididymis secretory sperm binding protein") adj2 deficien$).ti,ab,ot,kw,kf,hw.	233
5	Greenfield$ Disease.ti,ab,ot,kw,kf,hw.	6
6	(Cerebroside adj2 (Sulfatase or Sulphatase) adj2 Deficien$).ti,ab,ot,kw,kf,hw.	7
7	(cerebroside adj2 (sulfate or sulphate) adj2 storage disease).ti,ab,ot,kw,kf,hw.	0
8	((ASA or ESSPB or ARSA) adj2 Deficien$).ti,ab,ot,kw,kf,hw.	125
9	Cerebroside Deficien$.ti,ab,ot,kw,kf,hw.	0
10	((diffuse or metachromatic) adj3 (Cerebral or brain) adj3 sclerosis).ti,ab,ot,kw,kf,hw.	2362
11	((sulfatide or sulphatide) adj2 lipidosis).ti,ab,ot,kw,kf,hw.	18
12	(mckusick-25010 or mckusick25010).ti,ab,ot,kw,kf,hw.	0
13	(sulfatidosis or sulphatidosis).ti,ab,ot,kw,kf.	18
14	**or/1-13**	**4267**

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 5 May 2020, searched 13/05/2020

Number	Search terms	Number of results
1	MeSH descriptor: [Leukodystrophy, Metachromatic] this term only	5
2	(MLD and (gene* or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph* or leucodystroph*)):ti,ab,kw	77
3	(Metachromatic near/2 (leukoencephal* or leucoencephal* or leukodystroph* or leucodystroph*)):ti,ab,kw	12
4	(("Arylsulfatase A" or "Arylsulphatase A" or "epididymis secretory sperm binding protein") near/2 Deficien*):ti,ab,kw	2
5	Greenfield* Disease:ti,ab,kw	100
6	(Cerebroside near/2 (Sulfatase or Sulphatase) near/2 Deficien*):ti,ab,kw	1
7	(cerebroside near/2 (sulfate or sulphate) near/2 storage disease):ti,ab,kw	0
8	((ARSA or ASA or ESSBP) near/1 Deficien*):ti,ab,kw	1
9	Cerebroside Deficien*:ti,ab,kw	4
10	((diffuse or metachromatic) near/3 (Cerebral or brain) near/2 sclerosis):ti,ab,kw	7
11	((sulfatide or sulphatide) near/2 lipidosis):ti,ab,kw	0
12	(mckusick-25010 or mckusick25010):ti,ab,kw	0
13	(sulfatidosis or sulphatidosis):ti,ab,kw	0
14	**#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 in Trials**	**174**

NHS Economic Evaluation Database (NHS EED) (CRD): up to 31/03/2015, searched 14/05/2020

Number	Search terms	Number of results
1	MeSH DESCRIPTOR Leukodystrophy, Metachromatic IN NHSEED	0
2	(((MLD and (gene* or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph* or leucodystroph*)))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	1
3	(((Metachromatic near2 (leukoencephal* or leucoencephal* or leukodystroph* or leucodystroph*)))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
4	((((("Arylsulfatase A" or "arylsulphatase A" or "epididymis secretory sperm binding protein") near2 deficien*))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
5	(("Greenfield Disease" or "Greenfield Disease")) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
6	(((Cerebroside near2 (Sulfatase or Sulphatase) near2 Deficien*))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
7	(((cerebroside near2 (sulfate or sulphate) near2 "storage disease"))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
8	((((ASA or ESSPB or ARSA) near2 Deficien*))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
9	((("Cerebroside Deficiency" or "Cerebroside Deficiencies" or "Cerebroside Deficient"))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
10	((((diffuse or metachromatic) near3 (Cerebral or brain) near3 sclerosis))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
11	((((sulfatide or sulphatide) near2 lipidosis))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
12	(((mckusick-25010 or mckusick25010))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
13	(((sulfatidosis or sulphatidosis))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED	0
14	**#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13**	**1**

EconLit (EBSCO): 1886-07/05/2020, searched 14/05/2020

Number	Search terms	Number of results
1	AB ((MLD and (gene* or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph* or leucodystroph*))) OR TI ((MLD and (gene* or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph* or leucodystroph*)))	1

2	TX ((Metachromatic N2 (leukoencephal* or leucoencephal* or leukodystroph* or leucodystroph*))) OR TX ((("Arylsulfatase A" or "Arylsulphatase A" or "epididymis secretory sperm binding protein") N2 Deficien*)) OR TX Greenfield* Disease	0
3	TX ((Metachromatic N2 (leukoencephal* or leucoencephal* or leukodystroph* or leucodystroph*))) OR TX ((("Arylsulfatase A" or "Arylsulphatase A" or "epididymis secretory sperm binding protein") N2 Deficien*)) OR TX Greenfield* Disease	0
4	TX ((Cerebroside N2 (Sulfatase or Sulphatase) N2 Deficien*)) OR TX ((cerebroside N2 (sulfate or sulphate) N2 storage disease)) OR TX (((ARSA or ASA or ESSBP) N1 Deficien*))	0
5	TX Cerebroside Deficien* OR TX (((diffuse or metachromatic) N3 (Cerebral or brain) N2 sclerosis)) OR TX (((sulfatide or sulphatide) N2 lipidosis))	0
6	TX ((mckusick-25010 or mckusick25010)) OR TX ((sulfatidosis or sulphatidosis))	0
7	**S1 OR S2 OR S3 OR S4 OR S5 OR S6**	**1**

Science Citation Index (SCI) (Web of Science): 1988-07/05/2020, searched 14/05/2020

Number	Search terms	Number of results
18	**#14 not #17**	**1758**
17	#15 not (#15 and #16)	3284675
16	TS=(human)	3058157
15	TS=(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys)	4222219
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	2079
13	TS=(sulfatidosis or sulphatidosis)	5
12	TS=("mckusick-25010" or "mckusick25010")	0
11	TS=((sulfatide or sulphatide) NEAR/2 lipidosis)	3
10	TS=((diffuse or metachromatic) NEAR/3 (Cerebral or brain) NEAR/2 sclerosis)	9
9	TS=(Cerebroside NEAR/1 Deficien*)	10
8	TS=((ARSA or ASA or ESSBP) NEAR/1 Deficien*)	114
7	TS=(cerebroside NEAR/2 (sulfate or sulphate) NEAR/2 storage disease)	15
6	TS=(Cerebroside NEAR/2 (Sulfatase or Sulphatase) NEAR/2 Deficien*)	2
5	TS=(Greenfield* NEAR/1 Disease)	0
4	TS=(("Arylsulfatase A" or "Arylsulphatase A" or "epididymis secretory sperm binding protein") NEAR/2 Deficien*)	183
3	TS=(("Arylsulfatase A" or "Arylsulphatase A" or "epididymis secretory sperm binding protein") N2 Deficien*)	0
2	TS=(Metachromatic NEAR/2 (leukoencephal* or leucoencephal* or leukodystroph* or leucodystroph*))	1282
1	TS=(MLD and (gene* or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph* or leucodystroph*))	1053

NIH Clinicaltrials.gov (Internet): up to 19/05/2020, searched 19/05/2020
https://clinicaltrials.gov/

Search terms
sulfatidosis OR sulphatidosis OR mckusick-25010 OR mckusick25010 OR "sulfatide lipidosis" OR "sulphatide lipidosis" OR "diffuse brain sclerosis" OR "metachromatic brain sclerosis" OR "diffuse Cerebral sclerosis" OR "metachromatic Cerebral sclerosis" OR "Cerebroside Deficiency" OR "Cerebroside Deficiencies" OR "Cerebroside Deficient" OR "ARSA Deficiency" OR "ARSA Deficiencies" or "ARSA Deficient" OR "ESSBP Deficiency" OR "ESSBP Deficiencies" or "ESSBP Deficient" OR "Cerebroside Sulphatase storage disease" OR "Cerebroside Sulfatase storage disease" OR "Cerebroside Sulfatase Deficiency" OR "Cerebroside Sulphatase Deficiency" OR "Arylsulfatase A Deficiency" OR "Greenfield Disease" OR "Greenfields Disease" OR "Metachromatic leukoencephalopathy" OR "Metachromatic leucoencephalopathy" OR "Metachromatic leukodystrophy" OR "Metachromatic leucodystrophy" OR (MLD AND (gene OR genes OR genetic OR ARSA OR ASA OR arylsulfatase OR arylsulphatase OR leukodystrophy OR leucodystrophy))

Results identified through the above terms: 50

WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 19/05/2020, searched 19/05/2020
https://www.who.int/ictrp/en/

Unable to search WHO ICTRP on 19/05/2020. No longer accessible to non-WHO searchers due to COVID emergency access restrictions.

WORLDSymposium (Internet): 2018-2020, searched 04/06/2020

WORLDSymposium 2020
Poster Session Abstracts
https://worldsymposia.org/wp-content/uploads/WORLDSymposium2020-Poster-List.pdf

Search term	Hits
Metachromatic	5
MLD	1
Sulfatidosis	0
ESSBP	0
ARSA	0
Greenfield	0
Leukodystrophy	6
leucodystrophy	0
Total	**12**

Program
https://worldsymposia.org/wp-content/uploads/WORLDSymposium-2020-Program.pdf

Search term	Hits
Metachromatic	4
MLD	2
Sulfatidosis	0
ESSBP	0
ARSA	0
Greenfield	0
Leukodystrophy	4
leucodystrophy	0

Total	**8**

WORLDSymposium 2019
Poster Session Abstracts
https://www.worldsymposia.org/wp-content/uploads/WORLDSymposium-2019-Poster-List.pdf

Search term	Hits
Metachromatic	2
MLD	1
Sulfatidosis	0
ESSBP	0
ARSA	0
Greenfield	0
Leukodystrophy	3
leucodystrophy	0
Total	**6**

Program
https://worldsymposia.org/wp-content/uploads/WORLDSymposium-Program-2019.pdf

Search term	Hits
Metachromatic	3
MLD	0
Sulfatidosis	0
ESSBP	0
ARSA	0
Greenfield	0
Leukodystrophy	0
leucodystrophy	0
Total	**3**

WORLDSymposium 2018
Poster Session Abstracts
https://www.worldsymposia.org/wp-content/uploads/WORLDSymposium-2018-Poster-List.pdf

Search term	Hits
Metachromatic	5
MLD	0
Sulfatidosis	0
Sulfatidosis	0
ESSBP	0
ARSA	0
Greenfield	0
Leukodystrophy	7
leucodystrophy	0
Total	**12**

Program
https://worldsymposia.org/wp-content/uploads/WORLDSymposium-Program-2018.pdf

Search term	Hits
Metachromatic	1
MLD	1
Sulfatidosis	0
Sulfatidosis	0
ESSBP	0
ARSA	0
Greenfield	0
Leukodystrophy	3
leucodystrophy	0
Total	**5**

Orphanet Clinical Trials (Internet): up to 02/06/2020
Searched 02/06/2020
https://www.orpha.net/consor/cgi-bin/ResearchTrials_ClinicalTrials.php?lng=EN

Search term: Metachromatic Leukodystrophy
16 trial records.

15.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Details of all searches are given in the section above.

15.1.6 The inclusion and exclusion criteria.

Selection criteria used for published and unpublished studies

Inclusion criteria	

Population	Patients with early-onset metachromatic leukodystrophy (MLD), i.e. diagnosed aged ≤ 17yrs.
	Subgroups of interest within the main population included:
	• Symptomatic MLD
	• Pre-symptomatic MLD
	• Late Infantile MLD
	• Juvenile MLD
	  ○ Early Juvenile
	  ○ Late Juvenile
	Where populations included a mixed age group including patients with onset of disease >17yrs, studies were only included if data were reported separately for those with early-onset disease (i.e. symptoms appearing ≤ 17yrs).

Interventions	The intervention of interest was *ex-vivo* autologous lentiviral gene therapy, specifically OTL-200 (OTL-200). The following were included: • OTL-200 treatment arms in single arm studies • OTL-200 treatment arms in RCTs and cohort studies making a comparison with a relevant comparator treatment of interest. Comparator treatments of interest were: • Standard care/best supportive care/usual care* • Allogeneic haematopoietic stem cell transplantation (HSCT) The following were included: • Comparator treatment arms in single arm studies • Comparator treatment arms in RCT and cohort studies comparing the comparator treatments with each other or against the intervention of interest (i.e. OTL-200)

Outcomes	Studies must report at least one of the following specific outcomes which are relevant to the NICE scope (also based on outcomes from OTL-200 clinical studies): Mortality: • Overall survival (OS) expressed as a hazard ratio (HR), median time to event, or proportion (n/N; %) of patients surviving (if only number of deaths are reported this will be used to calculate the number surviving where possible) Progressive disease: • Proportion (n/N; %) of individuals with progressive disease (PD) • Median (range) time to progressive disease (PD) Motor function: • Proportion (n/N; %) of individuals with severe motor impairment • Median (range) time to severe motor impairment • Mean (SD)/median (range) age at time of severe motor impairment • Mean change (SD) from baseline in motor function measured using the following tools: • Gross Motor Function Classification System (GMFCS) • Gross Motor Function Measure (GMFM) • Gross motor function classification (GMFC-MLD) Neurological function: • Mean change (SD) from baseline in nerve conduction velocity (NCV) • Mean change (SD) from baseline in total score for brain magnetic resonance (MR) imaging (Loes score) and sub-scores (demyelination, atrophy and tigroid scores). Cognitive function: • Proportion (n/N; %) of individuals with cognitive impairment • Median (range) time to cognitive impairment • Mean change (SD) from baseline in neurocognitive function measured using the Intelligence Quotient (IQ) • Mean change (SD) from baseline in neurocognitive function measured using the Developmental Quotient (DQ) • Mean change (SD) from baseline in the Expressive Language Function Classification Arylsulfatase (ARSA) activity: • Change from baseline in ARSA activity in total peripheral blood mononuclear cells (PBMC) • Change from baseline in ARSA activity in leukocytes • Change from baseline in peripheral blood (PB) CD14+ cells • Change from baseline in cerebrospinal fluid (CSF) Health related quality of life (HRQoL): • Mean change (SD) from baseline in Caregiver Observed Metachromatic Leukodystrophy Functioning and Outcomes Reporting Tool (COMFORT) • Mean change (SD) from baseline in the (EQ-5D) Safety

	• Proportion (n/N; %) of patients experiencing the following safety outcomes (to include treatment related events, treatment emergent events, and all events, where separate data are available):
	  ○ Any adverse event
	  ○ Serious adverse events
	  ○ Fatal adverse events
	  ○ Any specific event occurring in ≥ 5% of patients in any one study arm
	Economic:
	• Health-related quality of life
	• Utilities
	• Costs and use of resources
	• For economic evaluations:
	  ○ Location of study
	  ○ Summary of model and comparators
	  ○ Patient population (key characteristics, average age)
	  ○ Costs (intervention and comparator)
	  ○ Patient outcomes (clinical outcomes, quality adjusted life expectancy (QALYs), life expectancy)
	  ○ Results (annual cost savings, annual savings per patient, incremental cost per QALY (ICER))

Study design	The following types of studies were included: • RCTs • Prospective or retrospective single arm studies with > 5 participants • Prospective or retrospective cohort studies with > 5 participants • Any type of economic evaluation (cost-effectiveness analysis (CEA), cost only comparison, budget impact analysis (BIA) or cost of illness (COI) study
Language restrictions	Searches were not limited by language.
Search dates	Databases from database inception to May 2020. Conferences 2018-2020. ClinicalTrials.gov (NIH): Up to 19 May 2020. Orphanet Clinical trials Search (Internet): up to 04 June 2020.

Exclusion criteria	
Population	Studies not reporting data on patients with early-onset metachromatic leukodystrophy (MLD), i.e. diagnosed aged ≤ 17yrs, including those where populations included a mixed age group including patients with onset of disease >17yrs, and data were not reported separately for those with early-onset disease (i.e. symptoms appearing ≤ 17yrs). Studies with ≤ 5 participants.
Interventions	Studies not reporting data on the listed interventions or comparators.
Outcomes	All other outcomes. Vector clone number (VCN) and % lentivirus (LV) + clone are outcomes only relevant for OTL-200 gene therapy, these will not be recorded as key outcomes.
Study design	All other study designs including, but not limited to, case reports, cross-sectional studies, animal studies or biochemical or cellular level investigations.
Language restrictions	Searches were not limited by language.
Search dates	None.

* Best supportive/symptomatic care can include any of the following including combinations of any of the following: Management of dystonia, infections, seizures (if required) or secretions; pain relief/sedative drugs (if required); feeding support (including gastrostomy); psychological and social support (including specialist schooling); coordination of the multidisciplinary team and community care; genetic advice and planning; and end of life care.

15.1.7 The data abstraction strategy.

Data extraction forms were individually designed and piloted using Microsoft Excel. Data extraction was performed by two reviewers working independently. Any discrepancies were resolved through discussion or the intervention of a third reviewer.

Studies were identified by the main study name/identifier. Where this was not available the surname and year of the first author of the main report/publication was used. To avoid the duplication of data where studies (or study populations) had multiple publications the most recent and complete report was used as the main reference, but additional details were extracted from the other publications, as necessary.

15.2 Appendix B2: Search strategy for adverse events

All outcomes were searched for in a single search, therefore please refer to Appendix B1.

15.3 Appendix B3: Search strategy for economic evidence

All outcomes were searched for in a single search, therefore please refer to Appendix B1.

15.4 Appendix B4: Resource identification, measurement and valuation

All outcomes were searched for in a single search, therefore please refer to Appendix B1.

Appendix C

Infantile health state GMFC 1

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You have stiffness in your muscles occasionally but you do not experience muscle contractions. You have normal posture. You experience pain at times. You do not have problems swallowing or gripping food. You do not have constipation or diarrhoea.
- You do not have seizures.
- You do not have any breathing difficulties.
- You can sit without support. You wobble slightly when you walk and move, are unsteady and sometimes fall. You have some trouble with balance.
- You have no problems seeing or hearing.
- You have no problems with sleep.
- You sometimes feel unhappy.

Infantile health state GMFC 2

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You have some stiffness in your muscles and you experience muscle contractions. You have normal posture. You experience significant pain. You sometimes have problems swallowing and gripping food. You vary between having constipation and diarrhoea at times.
- You do not have seizures.
- You do not have any breathing difficulties.
- You can sit without support. You wobble a lot when you walk and move, are unsteady and fall. You have a lot of difficulty with balance.
- You sometimes can't see properly and have trouble hearing sounds.
- You sometimes have disturbed sleep.
- You often feel unhappy.

Infantile health state GMFC 3

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You frequently have stiffness in your muscles and you experience muscle contractions. You have normal posture. You experience severe pain and receive medication for it. You are unable to swallow or grip food and may be fed through a tube. You vary between having severe constipation and diarrhoea.
- You do not have seizures.
- You sometimes have breathing difficulties.
- You can sit without support. You are unable to walk with or without support. You have no balance.
- You can't see properly and have trouble hearing sounds.
- You frequently have disturbed sleep.
- You feel very unhappy.

Infantile health state GMFC 4

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You have severe stiffness in your muscles and you experience frequent muscle contractions. Your head and body lean to one side. You experience severe pain and receive medication for it. You are unable to swallow or grip food. You are fed through a tube and are losing weight. You vary between having severe constipation and diarrhoea.
- You sometimes have seizures.
- You often have breathing difficulties.
- You are unable to sit without support. You are unable to walk with or without support. You have no balance.
- You can't see properly and have trouble hearing sounds.
- You have significant sleep disturbances.
- You cannot experience any feelings regarding your condition.

Infantile health state GMFC 5

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You have very poor muscle tone and you experience frequent muscle contractions. Your head and body lean to one side. You experience severe pain and receive medication for it. You are unable to swallow or grip food. You are fed through a tube and are losing weight. You vary between having severe constipation and diarrhoea.
- You have seizures very frequently.
- You often have breathing difficulties.
- You have some head control. You are unable to sit without support. You are unable to walk with or without support. You have no balance.
- You can't see or hear sounds.
- You are sleeping often during the day and night.
- You cannot experience any feelings regarding your condition.

Infantile health state GMFC 6

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You have no feeling in your muscles and you experience frequent muscle contractions. You are unable to move. You experience severe pain and receive medication for it. You are unable to swallow. You are fed through a tube and are losing weight. You vary between having severe constipation and diarrhoea.
- You have frequent seizures and require medication to control them.
- You have breathing difficulties all the time.
- You are lying in bed.
- You can't see or hear sounds.
- You are asleep most of the time.
- You cannot experience any feelings regarding your condition.

Juvenile state GMFC0 and Moderate Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This has affected your ability to think and understand the world.
- Your mobility is similar to people your own age.
- You do not have stiffness in your muscles and you do not experience muscle contractions. You have normal posture. You do not experience pain. You do not have problems swallowing or gripping food.
- Your brain functioning is worse than someone of your own age.
    - You sometimes forget things and have trouble concentrating on tasks or your interests outside and at home. You sometimes require help from family or friends to do tasks.
    - It takes you longer to learn new skills than it used to.
    - You are able to communicate using simple sentences and gestures, but it takes you longer to respond and form sentences. You can recognise your family members.
- You feel irritated when it takes you longer to do things you want to do. You worry about your condition in the future from time to time.
- You do not have seizures.
- You do not have any breathing difficulties.
- You have no problems with sleep.
- Your bowel and bladder function is normal. You do not have constipation or diarrhoea.

Juvenile state GMFC0 and Severe Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This has affected your ability to think and understand the world.
- Your mobility **is similar** to people your own age.
- You **do not** have stiffness in your muscles and you **do not** experience muscle contractions. You **have normal** posture. You **do not** experience pain. You **do not** have problems swallowing or gripping food.
- Your brain functioning **is much worse** than someone of your own age.
    - You **are very limited in the tasks you can do and they require considerable effort**.
    - You have **minimal ability** to learn new skills.
    - You **may** communicate **occasionally**, only with single words such as ‘mum’ or ‘dad’.
- You can express yourself by smiling or crying. You can recognise pictures and shapes. You can recognise your **family members**.
- You **feel very frustrated** when you are unable to do things you want to do. You are often unresponsive to your environment.
- You **do not** have seizures.
- You **do not** have any breathing difficulties.
- You have **no problems** with sleep.
- Your bowel and bladder function **is normal**. You **do not** have constipation or diarrhoea.

Juvenile state GMFC1 and Normal Cognitive Development

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **wobble slightly** when you walk and move, are unsteady and sometimes fall. You have **some trouble** with balance and running straight.
- You **do not** have stiffness in your muscles and you **do not** experience muscle contractions. You **have normal** posture. You **do not** experience pain. You **do not** have problems swallowing or gripping food.
- Your brain functioning **is similar** to someone of your own age.
    - You have **no problems** in remembering things or concentrating on tasks. You **don't need help** from family or friends to do tasks.
    - You **are able** to learn new skills.
    - You have **no problems** in communicating or interacting with others. You can recognise people **normally**.
- You **feel irritated** when you are unable to do things you want to do. You **worry** about your condition in the future from time to time.
- You **do not** have seizures.
- You **do not** have any breathing difficulties.
- You **sometimes** have trouble sleeping.
- Your bowel and bladder function **is normal**. You **do not** have constipation or diarrhoea.

Juvenile state GMFC2 and Normal Cognitive Development

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **can walk** with support and walking without support is not possible. You **wobble a lot** when you walk and move, are unsteady and fall. You **have a lot** of difficulty with balance and cannot run or take part in any sports/exercise.
- You **have some** stiffness in your muscles and you experience **occasional** muscle contractions. You **have normal** posture. You **have some** pain. You **do not** have problems swallowing but **have some** difficulty gripping food.
- Your brain functioning **is similar** to someone of your own age.
    - You have **no problems** in remembering things or concentrating on tasks. You d**on't need help** from family or friends to do tasks.
    - You **are able** to learn new skills.
    - You have **no problems** in communicating or interacting with others. You can recognise people **normally**.
- You **feel irritated and angry** that you are unable to do things you want to do. You **worry a lot** about your condition in the future from time to time.
- You **do not** have seizures.
- You **do not** have any breathing difficulties.
- You **have disturbed** sleep.
- Your bowel and bladder function **is normal**. You **do not** have constipation or diarrhoea.

Juvenile state GMFC3 and Normal Cognitive Development

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **are unable** to walk with or without support. You **have no** balance and cannot run or take part in any sports/exercise. You **need help** with washing and dressing yourself.
- You **have** stiffness in your muscles and you **sometimes** experience muscle contractions. You **have normal** posture. You **experience** pain and receive medication for it. You **have some problems** swallowing and gripping food and **may be fed through a tube**.
- Your brain functioning **is similar** to someone of your own age
  - You have no problems in remembering things or concentrating on tasks. You don't need help from family or friends to do tasks.
  - You are able to learn new skills.
  - You are able to communicate using full sentences and gestures. Due to stiffness in your muscles, it takes you longer to respond and form sentences. Sometimes, it may be hard for other people, other than your close ones, to understand you. You recognise people normally.
- You **feel irritated** and **angry** that you are unable to do things you want to do. You **often feel sad and upset** that you can't move around as you wish. You **worry a lot** about your condition in the future.
- You **sometimes** have seizures.
- You **do not** have any breathing difficulties.
- You **have significant** sleep disturbances.
- You **have** bowel and bladder problems where you lose control and have an accident. You **need to wear** a pad/nappy. You **vary** between having some constipation and diarrhoea.

Juvenile state GMFC4 and Normal Cognitive Development

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **are unable** to sit without support. You **are unable** to walk with or without support. You **have no** balance and cannot run or take part in any sports/exercise. You need help with washing and dressing yourself.
- You **have severe** stiffness in your muscles and you **experience frequent** muscle contractions. Your **head and body lean** to one side. You experience **severe** pain and receive medication for it. You **are unable** to swallow or grip food. You **are fed through a tube** and are losing weight.
- Your brain functioning **is similar** to someone of your own age.
    - You have no problems in remembering things or concentrating on tasks. You don't need help from family or friends to do tasks.
    - You are able to learn new skills.
    - You are able to communicate using simple sentences and gestures. Due to severe stiffness in your muscles, it takes you much longer to respond and form sentences. It is harder for other people, other than your close ones, to understand you. You are able to recognise people normally.
- You **feel irritated** and **angry** that you are unable to do things you want to do. You **often feel sad and upset** that you can't move around as you wish. You **worry a lot** about your condition in the future.
- You **have s**eizures frequently.
- You **sometimes** have breathing difficulties.
- You **have significant** sleep disturbances and need medication to sleep.
- You **have** incontinence and need to wear a pad/nappy. You **vary** between having severe constipation and diarrhoea.

Juvenile state GMFC1 and Moderate Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **wobble slightly** when you walk and move, are unsteady and sometimes fall. You have **some trouble** with balance and running straight.
- You **do not** have stiffness in your muscles and you **do not** experience muscle contractions. You **have normal** posture. You **do not** experience pain. You **do not** have problems swallowing or gripping food.
- Your brain functioning **is worse** than someone of your own age.
    - You **sometimes** forget things and have trouble concentrating on tasks or your interests outside and at home. You **sometimes** require help from family or friends to do tasks.
    - It takes you **longer** to learn new skills than it used to.
    - You are able to communicate using simple sentences and gestures, but it takes you **longer** to respond and form sentences. You can recognise your **family members**.
- You feel irritated when it takes you longer to do things you want to do. You worry about your condition in the future from time to time.
- You do not have seizures.
- You do not have any breathing difficulties.
- You sometimes have trouble sleeping.
- Your bowel and bladder function is normal. You do not have constipation or diarrhoea.

Juvenile state GMFC2 and Moderate Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **can walk** with support and walking without support is not possible. You **wobble a lot** when you walk and move, are unsteady and fall. You have **a lot of difficulty** with balance and cannot run or take part in any sports/exercise.
- You **have some** stiffness in your muscles and you experience **occasional** muscle contractions. You **have normal** posture. You have **some** pain. You **do not** have problems swallowing but have **some difficulty** gripping food.
- Your brain functioning **is worse** than someone of your own age.
    - You **sometimes** forget things and have trouble concentrating on tasks or your interests outside and at home. You **sometimes** require help from family or friends to do tasks.
    - It takes you **longer** to learn new skills than it used to.
    - You are able to communicate using simple sentences and gestures, but it takes you **longer** to respond and form sentences. You can recognise your **family members**.
- You feel irritated when it takes you longer to do things you want to do. You worry a lot about your condition in the future from time to time.
- You do not have seizures.
- You do not have any breathing difficulties.
- You have disturbed sleep.
- Your bowel and bladder function is normal. You do not have constipation or diarrhoea.

Juvenile state GMFC3 and Moderate Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **are unable** to walk with or without support. You have **no balance** and cannot run or take part in any sports/exercise. You **need help** with washing and dressing yourself.
- You **have** stiffness in your muscles and you **sometimes** experience muscle contractions. You **have normal** posture. You **experience** pain and receive medication for it. You have **some problems** swallowing and gripping food and **may be fed through a tube.**
- Your brain functioning **is worse** than someone of your own age.
    - You sometimes forget things and have trouble concentrating on tasks or your interests outside and at home. You sometimes require help from family or friends to do tasks.
    - It takes you longer to learn new skills than it used to.
    - You are able to communicate using some simple sentences and gestures. Due to stiffness in your muscles, it takes you longer to respond and form sentences. Sometimes, it may be hard for other people, other than your close ones, to understand you. You can recognise your family members.
- You **feel irritated and angry** that it takes you longer to do things you want to do. You **worry a lot** about your condition in the future.
- You **sometimes** have seizures.
- You **do not** have any breathing difficulties.
- You **have significant** sleep disturbances.
- You **have** bowel and bladder problems where you lose control and have an accident. You need to wear a pad/nappy. You **vary** between having some constipation and diarrhoea.

Juvenile state GMFC4 and Moderate Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You are unable to sit without support. You are unable to walk with or without support. You have no balance and cannot run or take part in any sports/exercise. You need help with washing and dressing yourself.
- You have severe stiffness in your muscles and you experience frequent muscle contractions. Your head and body lean to one side. You experience severe pain and receive medication for it. You are unable to swallow or grip food. You are fed through a tube and are losing weight.
- Your brain functioning is worse than someone of your own age.
    - You **sometimes** forget things and have trouble concentrating on tasks or your interests outside and at home. You **sometimes** require help from family or friends to do tasks.
    - It takes you **longer** to learn new skills than it used to.
    - You are able to communicate using **some** simple sentences and gestures. **Due to severe stiffness in your muscles**, it takes you **much longer** to respond and form sentences. **It is harder for other people, other than your close ones, to understand you**. You can recognise your **family members**.
- You **feel irritated and angry** that it takes you much longer to do things you want to do. You **often feel sad and upset** that you can't move around as easily as you wish. You **worry a lot** about your condition in the future.
- You **have** seizures **frequently**.
- You **sometimes** have breathing difficulties.
- You **have significant** sleep disturbances and need medication to sleep.
- You **have incontinence** and need to wear a pad/nappy. You **vary** between having severe constipation and diarrhoea.

Juvenile state GMFC5 and Moderate Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You have **some** head control. You **are unable** to sit without support. You **are unable** to walk with or without support. You have **no balance** and cannot run or take part in any sports/exercise. You **are unable** to wash and dress yourself.
- You **have very severe stiffness in your muscles** and you experience **frequent** muscle contractions. Your **head and body lean** to one side. You experience **severe** pain and receive medication for it. You **are unable** to swallow or grip food. You **are fed through a tube** and are losing weight.
- Your brain functioning **is worse** than someone of your own age.
    - You sometimes forget things and have trouble concentrating on tasks or your interests outside and at home. You sometimes require help from family or friends to do tasks.
    - It takes you longer to learn new skills than it used to.
    - You are able to communicate using some simple groans and gestures. Due to very severe stiffness in your muscles, it takes you much longer and more effort to respond. It is harder for other people, other than your close ones, to understand you. You can recognise your family members.
- You feel irritated and angry that it takes you much longer to do things you want to do. You often feel sad and upset that you can't move around as easily as you wish. You worry a lot about your condition in the future.
- You have seizures very frequently.
- You often have breathing difficulties.
- You are sleeping often during the day and night.
- You have incontinence and need to wear a pad/nappy. You vary between having severe constipation and diarrhoea.

Juvenile state GMFC6 and Moderate Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You are unable to move.
- You have little feeling in your muscles and experience frequent muscle contractions. You experience severe pain and receive medication for it. You are unable to swallow. You are fed through a tube and are losing weight.
- Your brain functioning is worse than someone of your own age.
    - You **sometimes** forget things and have trouble concentrating on tasks or your interests outside and at home. You **sometimes** require help from family or friends to do tasks.
    - It takes you **longer** to learn new skills than it used to.
    - You are able to communicate using **some** simple gestures. **Due to little feeling in your muscles**, it takes you **much longer and a lot more effort** to respond and use gestures. **It is very hard for other people, other than your close ones, to understand you**. You can recognise your **family members**.
- You **feel irritated and angry** that you are unable to do things you want to do. You **feel sad and upset** that you can't move around.
- You **have frequent** seizures and **require medication** to control them.
- You **have** breathing difficulties all the time.
- You **are asleep most** of the time.
- You **have incontinence** and need to wear a pad/nappy. You **vary** between having severe constipation and diarrhoea.

Juvenile state GMFC1 and Severe Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **wobble slightly** when you walk and move, are unsteady and sometimes fall. You **have some** trouble with balance and running straight.
- You **do not** have stiffness in your muscles and you **do not** experience muscle contractions. You **have normal** posture. You **do not** experience pain. You **do not** have problems swallowing or gripping food.
- Your brain functioning **is much worse** than people your own age.
    - You are very limited in the tasks you can do and they require considerable effort.
    - You have minimal ability to learn new skills.
    - You may communicate occasionally, only with single words such as 'mum' or 'dad'. You can express yourself by smiling or crying. You can recognise pictures and shapes. You can recognise your family members.
- You feel very frustrated when you are unable to do things you want to do. You are often unresponsive to your environment.
- You do not have seizures.
- You do not have any breathing difficulties.
- You sometimes have trouble sleeping.
- Your bowel and bladder function is normal. You do not have constipation or diarrhoea.

Juvenile state GMFC1 and Severe Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **can walk** with support and walking without support is not possible. You **wobble a lot** when you walk and move, are unsteady and fall. You have **a lot of difficulty** with balance and cannot run or take part in any sports/exercise.
- You **have some** stiffness in your muscles and you **experience occasional** muscle contractions. You **have normal** posture. You have **some** pain. You **do not** have problems swallowing but **have some** difficulty gripping food.
- Your brain functioning **is much worse** than people your own age.
    - You are very limited in the tasks you can do and they require considerable effort.
    - You have minimal ability to learn new skills.
    - You may communicate only with single words such as 'mum' or 'dad'. You can express yourself by smiling or crying. You can recognise pictures and shapes. You can recognise your family members.
- You feel very frustrated when you are unable to do things you want to do. You are often unresponsive to your environment.
- You do not have seizures.
- You do not have any breathing difficulties.
- You have disturbed sleep.
- Your bowel and bladder function is normal. You do not have constipation or diarrhoea.

Juvenile state GMFC3 and Severe Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **can sit** without support. You **are unable** to walk with or without support. You have **no balance** and cannot run or take part in any sports/exercise. You **need help** with washing and dressing yourself.
- You **have stiffness** in your muscles and you **sometimes** experience muscle contractions. You **have normal** posture. You **experience pain** and receive medication for it. You have **some problems** swallowing and gripping food and **may be fed through a tube.**
- Your brain functioning **is much worse** than people your own age .
    - You are very limited in the tasks you can do and they require considerable effort.
    - You have minimal ability to learn new skills.
    - You may communicate only with single words such as 'mum' or 'dad'. Due to stiffness in your muscles, it takes you longer to respond and form words. You can express yourself by smiling or crying. You can recognise pictures and shapes. You can recognise your family members.
- You feel very frustrated when you are unable to do things you want to do. You are often unresponsive to your environment.
- You sometimes have seizures.
- You do not have any breathing difficulties.
- You have significant sleep disturbances.
- You have bowel and bladder problems where you lose control and have an accident. You need to wear a pad/nappy. You vary between having some constipation and diarrhoea.

Juvenile state GMFC4 and Severe Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You are unable to sit without support. You are unable to walk with or without support. You have no balance and cannot run or take part in any sports/exercise. You need help with washing and dressing yourself.
- You have severe stiffness in your muscles and you experience frequent muscle contractions. Your head and body lean to one side. You experience severe pain and receive medication for it. You are unable to swallow or grip food. You are fed through a tube and are losing weight.
- Your brain functioning is much worse than people your own age.
    - You are very limited in the tasks you can do and they require considerable effort.
    - You have minimal ability to learn new skills.
    - You may communicate only with single words such as ‘mum’ or ‘dad’. Due to severe stiffness in your muscles, it takes you much longer to respond and form words. You can express yourself by smiling or crying. You can recognise pictures and shapes. You can recognise your family members.
- You feel very frustrated when you are unable to do things you want to do. You are often unresponsive to your environment.
- You have seizures frequently.
- You sometimes have breathing difficulties.
- You have significant sleep disturbances and need medication to sleep.
- You have incontinence and need to wear a pad/nappy. You vary between having severe constipation and diarrhoea.

Juvenile state GMFC5 and Severe Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You have some head control. You are unable to sit without support. You are unable to walk with or without support. You have no balance and cannot run or take part in any sports/exercise. You are unable to wash and dress yourself.
- You have very severe stiffness in your muscles and you experience frequent muscle contractions. Your head and body lean to one side. You experience severe pain and receive medication for it. You are unable to swallow or grip food. You are fed through a tube and are losing weight.
- Your brain functioning is much worse than people your own age.
    - You are very limited in the tasks you can do and they require considerable effort.
    - You have minimal ability to learn new skills.
    - You may communicate using some simple groans. Due to very severe stiffness in your muscles, it takes you much longer and more effort to respond and form groans. You can express yourself by smiling or crying. You can recognise pictures and shapes. You can recognise your family members.
- You feel very frustrated when you are unable to do things you want to do. You are often unresponsive to your environment.
- You have seizures very frequently.
- You often have breathing difficulties.
- You are sleeping often during the day and night.
- You have incontinence and need to wear a pad/nappy. You vary between having severe constipation and diarrhoea.

Juvenile state GMFC6 and Severe Cognitive Impairment

- You have a life-threatening disease which is affecting your nervous system (your brain and nerves). This affects your movement, your ability to think and understand the world and your control over your body.
- You **are unable** to move.
- You have **little feeling** in your muscles and experience **frequent** muscle contractions. You experience **severe** pain and receive medication for it. You **are unable** to swallow. You **are fed through a tube** and are losing weight.
- Your brain functioning **is much worse** than people your own age.
    - You are very limited in the tasks you can do and they require considerable effort.
    - You have no ability to learn new skills.
    - You can communicate using simple facial expressions and movements only. You can express yourself by smiling or crying. You can recognise pictures and shapes. You can recognise some of your family members.
- You can feel some emotions such as happiness or discomfort. You have limited awareness of your environment.
- You have frequent seizures and require medication to control them.
- You have breathing difficulties all the time.
- You are asleep most of the time.
- You have incontinence and need to wear a pad/nappy. You vary between having severe constipation and diarrhoea.

Appendix D

Appendix D1 OTL-200 INDICATED POPULATION dataset Full-/Partial-Responder Classification

Patient ID	Disease Variant	Age at entry into GMFC-MLD 0	Age at entry into GMFC-MLD 1	Age at entry into GMFC-MLD 2	Age at entry into GMFC-MLD 3	Age at entry into GMFC-MLD 4	Age at entry into GMFC-MLD 5	Age at entry into GMFC-MLD 6	Responder Status
MLD01	PS LI			[redacted]					Partial
MLD02	PS LI	[redacted]							Full
MLD03	PS LI	[redacted]							Full
MLD05	PS LI	[redacted]							Full
MLD06	PS LI	[redacted]	[redacted]						Partial
MLD07	PS LI			[redacted]	[redacted]	[redacted]			Partial
MLD15	PS LI	[redacted]							Full
MLD22	PS LI		[redacted]	[redacted]					Partial
MLD-HE01	PS LI		[redacted]						Partial
MLD-HE02	PS LI		[redacted]						Partial
MLD-HE03	PS LI	[redacted]							Full
MLD-CUP01	PS LI			[redacted]					Partial
MLD-CUP02	PS LI			[redacted]					Partial
MLD-CUP03	PS LI	[redacted]							Full
MLD-CUP05	PS LI		[redacted]						Partial
MLD09	PS EJ	[redacted]							Full
MLD12	PS EJ	[redacted]							Full

MLD16	PS EJ	[redacted]							Full
MLD20	PS EJ	[redacted]	[redacted]						Partial
MLD-CUP04	PS EJ	[redacted]							Partial (death)
MLD08	ES EJ		[redacted]	[redacted]					Partial
MLD13	ES EJ	[redacted]	[redacted]	[redacted]		[redacted]			Partial
MLD14	ES EJ		[redacted]	[redacted]	[redacted]				Partial
MLD17	ES EJ		[redacted]	[redacted]					Partial
MLD-C02	ES EJ	[redacted]	[redacted]						Partial

*Previous GMFC-MLD assessments excluded due to invalid “improving” GMFC-MLD scores.

Appendix D2. PS EJ BSC Cognitive Sub-state Distribution by GMFC-MLD Stage.

Cognitive Sub-state distribution	**Normal/mild Cognitive Function (DQ ≥ 70)**	**Moderately Cognitive Impairment (70 > DQ ≥ 55)**	**Severe Cognitive Impairment (DQ < 55)**	**Time until Cognitive Decline (months)**
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for “After Cognitive Decline: GMFC-MLD 0”, “GMFC-MLD 1”, “GMFC-MLD 2”, and “GMFC-MLD 6” provided by results of SEE (11). Values for GMFC-MLD 3, 4 and 5 derived from an assumed linear decline between known values. Values for “Before Cognitive Decline: GMFC-MLD 0” assumed based on prior clinical expert input.
*Time until cognitive decline derived from difference between 57 mo. (average EJ onset occurring between 30 months and 7 years) and 45 months (age at PS EJ model entry).

Appendix D3. PS EJ OTL-200 Full-Responder Cognitive Sub-state Distribution by GMFC-MLD Stage.

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for GMFC-MLD 5 and GMFC-MLD 6 assumed to utilize BSC values. All other cognitive distribution values informed by clinical trial DQp data and clinical expert opinion.
*Time until cognitive decline derived from difference between 16 years (max. follow-up time in Orchard Therapeutics clinical trial) and 45 months (age at PS EJ model entry) based on clinical expert advice.

Appendix D4. PS EJ OTL-200 Partial-Responder Cognitive Sub-state Distribution by GMFC-MLD Stage.

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for GMFC-MLD 5 and GMFC-MLD 6 assumed to utilize BSC values. All other cognitive distribution values informed by clinical trial DQp data and clinical expert opinion.
*Time until cognitive decline derived from difference between 16 years (max. follow-up time in Orchard Therapeutics clinical trial) and 45 months (age at PS EJ model entry) based on clinical expert advice.

Appendix D5. ES EJ BSC Cognitive Sub-state Distribution by GMFC-MLD Stage.

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for “After Cognitive Decline: GMFC-MLD 0”, “GMFC-MLD 1”, “GMFC-MLD 2”, and “GMFC-MLD 6” provided by results of SEE (11). Values for GMFC-MLD 3, 4 and 5 derived from an assumed linear decline between known values. Values for “Before Cognitive Decline: GMFC-MLD 0” assumed based on prior clinical expert input.
*Time until cognitive decline conservatively derived from difference between 57 mo. (average EJ onset occurring between 30 months and 7 years) and 45 months (age at PS EJ model entry).

Appendix D6. ES EJ OTL-200 Full-Responder Cognitive Sub-state Distribution by GMFC-MLD Stage.

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for GMFC-MLD 5 and GMFC-MLD 6 assumed to utilize BSC values. All other cognitive distribution values informed by clinical trial DQp data and clinical expert opinion.
*Time until cognitive decline derived from difference between 16 years (max. follow-up time in Orchard Therapeutics clinical trial) and 80 months (age at ES EJ model entry) based on clinical expert advice.

Appendix D7. ES EJ OTL-200 Partial-Responder Cognitive Sub-state Distribution by GMFC-MLD Stage.

Cognitive Sub-state distribution	Normal/mild Cognitive Function (DQ ≥ 70)	Moderately Cognitive Impairment (70 > DQ ≥ 55)	Severe Cognitive Impairment (DQ < 55)	Time until Cognitive Decline (months)
Before Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	[redacted]
After Cognitive Decline: GMFC-MLD 0	[redacted]	[redacted]	[redacted]	
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	

Note: Distributions for GMFC-MLD 5 and GMFC-MLD 6 assumed to utilize BSC values. All other cognitive distribution values informed by clinical trial DQp data and clinical expert opinion.
*Time until cognitive decline derived from difference between 16 years (max. follow-up time in Orchard Therapeutics clinical trial) and 80 months (age at ES EJ model entry) based on clinical expert advice.

Appendix E

The Orchard Therapeutics process for the choice and qualification of OTL-200 Treatment Centres is based on the centres fulfilling objective clinical, regulatory and logistical criteria:

[redacted]

Appendix F

Parametric Extrapolation Summary

Objectives:

- Fit parametric curves to the underlying MLD survival data from the Orchard Therapeutics TIGET Natural History Study to extrapolate survival beyond the trial period.
- Assess variance around fitted parametric curves for their inclusion in the probabilistic sensitivity analysis.

Underlying Data:

For each of the disease subtypes (i.e. LI and EJ) in the Orchard Therapeutics TIGET Natural History Study, IPD was generated based on age at death or censoring. This underlying data can be found in the "Parametric Extrapolation Data" workbook in the 'LI_IPD' and 'EJ_IPD' tab.

Extrapolation Process:

Parametric curve fitting and extrapolation beyond the trial period utilise the attached R code that can be found in the "Parametric Extrapolation Data" workbook in the 'R Code' tab. Parametric extrapolation and curve fitting is performed using the '*flexsurv'* and *'survival' R* packages. The R code used can be found in the "Parametric Extrapolation Data" workbook in the 'R_Code' tab.

Extrapolation Output:

The R code outputs the parameter estimates from the parametric curve fitting into a .csv file. AIC, BIC, and variance-covariance matrices for each curve are also output to inform the mathematical best fit and variance around the parameter estimates. Output from the R code can be found in the "Parametric Extrapolation Data" workbook in the 'LI_Parameters' and 'EJ_Parameters' tabs.

Implementation in Model:

Parametric curve parameters are input into the 'NHx_Extrapolation' tab of the economic model in the corresponding cell. Parametric curve survival estimates are calculated within Excel using the provided parameters. Live survival estimates are bounded so they cannot be greater than the general population survival.

Variance-covariance matrices are provided on the 'Parameters' tab of the economic model for use in the PSA.

Probabilistic Sensitivity Analysis (PSA):

After parametric extrapolation of digitized survival curves for the MLD economic model, resulting in 7 extrapolated survival curves for the LI and EJ natural

history survival sources, variance covariance matrices for each parametric curve were generated to assess the level of variability around the curve parameters. Due to the small sample size and limited number of deaths reported, especially in the EJ population, the variance was bounded in the PSA to prevent the generation of invalid curve parameters (e.g. prevention of negative parameters values where required).

During the PSA, the variance covariance matrix for the modelled parametric curve was transformed using the Cholesky decomposition. The resulting matrix was used to vary the parametric curve parameters and generate new curve parameters based on the variability surrounding the initial curve fitting.

17 Related procedures for evidence submission

17.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

17.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly

Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

17.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by

equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Checklist of Confidential Information

Document; Page*	Nature of confidential information	Rationale for confidential status (or status change)	Timeframe of confidentiality restriction (or date of change)‡
4, 9-15, 17-20, 27-34, 38-43, 45, 47-51, 56, 59-60, 62-63, 69-70, 78-83, 86-88	☐ Commercial in confidence† ☒ Academic in confidence† ☐ Depersonalised data	Unpublished data from an a post-hoc analysis of the results of the clinical trials	The results of the post-hoc analysis have not been published. A manuscript is under development, but the company is not aware of approximate publication timelines. The company will update NICE as soon as these become available.
22, 28, 33, 37, 39, 42, 44-46, 48, 51-54 65, 67-68, 70-72, 74	☒ Commercial in confidence ☐ Academic in confidence ☐ Depersonalised data	Incremental costs/QALYs, ICERs, budget impact, statements from clinicians and details about the new-born screening are commercial in confidence information. The utility values are academic in confidence information and will be the subject of a future publication.	Incremental costs/QALYs, ICERs, budget impact, statements from clinicians and details about the new-born screening are indefinite as related to commercial information The utility values will be unredacted once the manuscript has been accepted for publication (estimated Q2 2021).

* Reference page(s) of any document where the confidential information appears.

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‡Please state whether the timeframe given is exact or approximate. For academic in confidence material, state either the date and title of the conference at which the information will be made public, or the date of submission and title of the journal to which the relevant paper has been submitted, together with the journal's stated turnaround time.

I confirm that any confidential sections of the submitted documents have been underlined and highlighted, and that if any change occurs to the above information a new checklist will be submitted. Over and above this checklist, it is the company's responsibility to provide updated marked and redacted documents to NICE if/when confidential marking has changed in any of their previously submitted documents. Please contact your Project Team if you have any queries at HST@NICE.ORG.UK

Name of person completing checklist: Andrew Olaye
Contact details (☎/email): +447584531747 / Andrew.olaye@orchard-tx.com
Date: 27th January, 2021

NICE National Institute for Health and Care Excellence

Patient organisation submission

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**ArchAngel MLD Trust**

2. Name of organisation	ArchAngel MLD Trust
3. Job title or position	Chairperson
4a. Brief description of the organisation (including who funds it). How many members does it have?	ArchAngel MLD Trust is an unincorporated association governed by a constitution. Registered Charity Number 1157825. The Trust is run by volunteer charity trustees appointed to hold office for a fixed term of one year. It is predominantly funded by charitable donations from members of the public. The Trust was founded in 2014 by a family affected by Metachromatic Leukodystrophy in their desire to help others facing this rare and terminal illness. The Trust's fundamental aims are to support medical teams around the world who are working to help people with MLD and to award private grants to UK families with MLD affected children. The Trust is connected to 38 UK families/44 patients (including those with deceased children). ArchAngel works in close collaboration with The MPS Society and MLD Support Association UK, each of whom offer different support services to the MLD patient community. ArchAngel is also spearheading a campaign to have all UK babies screened for MLD (and other rare diseases) at birth and is therefore working within a number of international MLD and rare disease collaborations, including MLD Foundation, Cure MLD, MLD US RUSP Alliance and MLD European Alliance.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	In December 2019 ArchAngel received a grant of £5000 from Orchard Therapeutics in support of newborn screening research across all inherited metabolic disorders, not specifically for MLD newborn screening. In August 2020 ArchAngel MLD Trust, The MPS Society and MLD Support Association UK jointly received a grant from Orchard Therapeutics of £11,600 in August 2020 to carry out an MLD patient and caregiver burden survey.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Trust is connected to 38 UK families/44 patients (including deceased) and has financially supported 21 patients to date, including the funding of specialist equipment, home adaptations, physical therapies and respite care. This has enabled Trustees to develop many close relationships and an in-depth knowledge of the struggles and many challenges faced by the UK MLD community, both within and outside of the health service. The chairperson of ArchAngel is the parent of an Early Juvenile MLD patient who received Gene Therapy for MLD in 2014. Not only are the family connected to over 400 MLD families worldwide, the family are also closely connected to 33 other families from around the world who have received Gene Therapy, both as part of a clinical trial and on compassionate grounds. This has afforded a unique insight into the advantages/disadvantages of the treatment over a 10-year period and the experiences of many families with multiple affected children, who can directly compare treated and untreated siblings. ArchAngel MLD Trust works closely with The MPS Society and MLD Support Association UK and these three patient organisations have collectively commissioned Rare Disease Research Partners to conduct a caregiver study to increase understanding of the natural history of MLD, its impact and burden on patients and their families and the effects of gene therapy. The survey engaged 20 families, representing 24 children and including 6 patients treated with Gene Therapy. It is worth noting that more than half of the known UK MLD caregivers took time to partake in this survey, a significant number considering the fact that their child/ward would **not** be eligible to receive the treatment being assessed. Many communicated their strong desire to help prevent future children and families from having to endure the same excruciating suffering as their own children and families have. ArchAngel is also a member of a number of international organisations, including MLD Foundation, Cure MLD, MLD US RUSP Alliance and MLD European Alliance, which has facilitated further knowledge from close working relationships with expert clinical colleagues from both the UK and across the globe.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	In our experience and consistent with the results of the long-term natural history study (Biffi et al), MLD is a rare disease of the utmost severity. Patients face immeasurable suffering and certain premature death. The accumulation of toxic material (due to lack of ARSA enzyme) causes a breakdown in communication between the nerves and brain, causing destruction of the Central and Peripheral Nervous Systems. Children rapidly lose the ability to walk, talk, swallow, see, hear and become doubly incontinent; they develop serious muscular and skeletal complications, including scoliosis and hip dislocations; they go on to suffer epilepsy and dementia; and can endure a final protracted period of suffering in an unresponsive state. With an autosomal recessive inheritance pattern, families have a 1 in 4 chance of an affected child, resulting in many families with more than one affected child. The Late Infantile (LI) sub-type of MLD is particularly aggressive (symptom onset at less than 30 months). A typical diagnostic journey is approximately 11 months (survey p.21) and within that timeframe most parents report a rapid, unrelenting motor and cognitive decline. Most LI affected children die by the age of 5. Early Juvenile (EJ) patients follow the same trajectory, however onset is later (between 30 months and 6 years of age). Diagnosis of the EJ sub-type is more challenging, due to the initial presentation of a gait disturbance or behavioural issue at school, and children are commonly initially misdiagnosed. EJ children have a typical prognosis of death in teenage years. There are also Late Juvenile (symptom onset between 7 and 16 years) and Adult (symptom onset at 17 years of age or older) sub-types of this disease, which progress at a slower pace but ultimately lead to the same total loss of function. However, since the technology under assessment is not applicable to those patients at the present time, the feedback in this submission pertains to our knowledge and experience of the LI and EJ sub-types only. **MLD PATIENTS EXPERIENCE A RAPID ONSET OF DISEASE AND SUFFER MULTIPLE INCAPACITATING SYMPTOMS** In our survey, parents of untreated LI children describe a rapid progression of symptoms around the time of diagnosis (10 children diagnosed between the ages of 2.5-2.7 years). One parent describes how their child went from crawling up and down stairs to being completely bedbound over a period of six months from diagnosis (p.22). The cumulative impact of symptoms is harrowing and the severity of MLD has been summarised by these parents: Father of LI child aged 5: ***"[Child's] life has been a torture, an absolute torture."*** (survey p.40) Mother of EJ child aged 12: ***"She's being tortured, basically. She is. That's what this disease is doing to her. It's torturing her little body. And we have to sit and watch that."*** (survey p.53) **Loss of Mobility** Issues with mobility are often a first indication of disease. Total loss of mobility can happen within a period of months and generally takes less than a year. Over 60% of LI caregivers surveyed reported their child requiring a wheelchair at diagnosis

	and **100% of respondents to reported wheelchair dependence or total immobility at present/time of death.** 100% of EJ caregivers reported issues with walking as a first symptoms and **100% report current wheelchair dependence or total immobility at present/time of death.** **Loss of Communication** Despite all children tending to meet their early developmental milestones for speech, at the time of survey, **80% of LI children (mean age 5.7 years) had lost their ability to speak**. Furthermore, **60% were no longer able to communicate pain or discomfort and one child was described as "unresponsive**". 100% of EJ patients were already experiencing Dysarthria (difficulty producing speech) at diagnosis and **100% of EJ patients are now unable to communicate/unresponsive.** **Loss of Ability to Swallow** Parents identify difficulty swallowing or risk of choking as a common first symptom, as seen in 40% of LI patients in our caregiver survey. Children quickly progress to a total inability to swallow and at the time of survey **100% of LI and EJ patients were fed by either gastrostomy or nasogastric tube.** Clinicians report that gastrointestinal problems are extremely prevalent and that patients persistently struggle to gain weight and thrive. Many patients struggle to tolerate gastrostomy feeds and members of all the patient communities we are connected to frequently reach out for advice on difficulties associated with tube feeding. One survey respondent described episodes of vomiting and diarrhoea 10—15 times a day and vomiting episodes so severe that they required hospital treatment: ***"I aspirate, we syringe his tummy before every feed, because he's starting to be sick a lot…and we've been in the hospital twice with some serious sickness where he had to go onto a drip."***(p.30). **Loss of Continence** **All patients progress to double incontinence by the end of life.** Constipation and urinary retention are also common symptoms in MLD affected children and can require invasive management. Survey respondents reported 38% of LI patients requiring urinary catheterisation and 25% bowel enemas. 100% of EJ patients suffer constipation and 33% require urinary catheterisation. **Loss of Eyesight & Hearing** As eye and ear nerve pathways deteriorate, patients develop vision difficulties, which can lead to blindness and hearing problems, which can lead to deafness. This progression is extremely difficult to track, since carers see little point in formal assessment. Their greatest concern is whether their child is visually and audibly aware of interaction with others and world around them. One surveyed LI parent articulates their experience: ***"He can hear and he can see but he drifts in and out of focusing. His eyes tend to roll up into his head so to what degree he can see we don't really know but he can recognise the face of [family]."***(p.29). **100% of EJ patients are blind.** **Respiratory Issues**

	Breathing can become difficult for children in latter stages of the disease and one parent surveyed described their LI child as "really struggling with his airways". Excess secretions are a significant problem, with **80% of LI patients requiring medication and 75% requiring regular suctioning**. **100% of EJ patients experience aspiration, excess secretions and frequent chest infections.** Hospitalisations due to chest infections are widely discussed within patient communities and requests are made to the charity each winter for 'shaky vests', to help clear secretions/mucus in an attempt to stave off infection. **Pain & Muscular/Skeletal Complications** As MLD progresses, the suffering caused by loss of previously acquired abilities is exacerbated by the development of major muscular and skeletal changes, causing significant pain and presenting multiple challenges in the management of them. MLD children inevitably suffer with **chronic Dystonia (muscle spasms) and Spasticity/Hypertonia, as seen in our survey where 80% of LI and 100% of EJ patients reported both**. Clinical teams report that pain is multifactorial and very difficult to treat/palliate due to its multifactorial nature (and also the fact that MLD children often cannot communicate its location). They concur that much pain results from the muscle spasms/spasticity that are part of the condition, but can also be contributed to by skeletal pain, including scoliosis and hip dislocations which cause prolonged periods of excruciating pain. **40% of LI patients had developed scoliosis and hip dislocation at the time of survey. 100% of EJ had scoliosis, Dystonia, Spasticity/Hypertonia and 67% had hip dislocation.** One parent reports: ***"She would take a long time to fall asleep and she would cry a lot as well. She was in pain, but it wasn't obvious where she might be in pain."*** Pain not only prevents MLD children from sleeping, as a consequence parents and siblings can all be very sleep deprived. Patients also suffer pain from constipation, gastro-oesophageal reflux and from peripheral neuropathy (neuropathic pain). Since toxic material accumulates in other areas of the body, including liver, gall bladder, kidneys, and spleen, parents in the wider patient community frequently speculate on whether pain is emanating from these sites. Despite the use of multiple medications, achieving physical comfort can still be extremely challenging and parents appeal to ArchAngel for financial support with bespoke seating, extra positioning/sleeping aids, and extra physiotherapy, as their child's needs cannot be met by standard equipment and therapy provision. **Neurological Issues** Seizures, anxiety and/or panic are the most consistent neurological symptoms experienced by patients, with **80% of LI/67% of EJ surveyed patients receiving anti-seizure medication and anxiety experienced by 60% of LI /67% of EJ patients.** Disruption to the autonomic nervous system also causes issues with temperature regulation (LI 50%; EJ 100%), sleep regulation (LI 50%; EJ 67%) and uncontrolled crying (LI 50%; EJ 33%). Dysfunction in the cells that detect sensations such as touch, pain, heat, and sound (the peripheral nervous system) also cause distress to MLD patients, as reported in LI 40%; EJ 67% survey participants. **Cognition & Impact on Education**

Whilst most children meet their early learning developmental milestones, most require support in learning from an early age. Due to the extensive range of symptoms and difficulties experienced by patients, it soon becomes impractical for the majority of children to attend school. **Our survey reported all LI children needed 1:1 or 2:1 support starting at an average age of 2.4 years; EJ children required this at an average of 6.3 years.** Of 7 LI children, only 2 were able to attend a specialist school, with the remaining 5 children needing to remain in the home environment. The EJ cohort attended specialist schools, however all required EHCP plans from the age of 6 years, which include 2:1 support, personal care, specialist equipment and transport. Many parents known to the charity describe school as more of a 'babysitting service', as their children are unable to participate in or engage with their environment.

MLD PATIENTS CREATE A SIGNIFICANT BURDEN TO CAREGIVERS, RESULTING IN BROAD DETRIMENTAL IMPACT

It is abundantly clear that MLD affected children have little or no quality of life, depending upon their stage of disease, and this inevitably impacts enormously on each patient's family. With parents undertaking the majority of care duties, their lives are entirely dominated by MLD. This has an extremely detrimental effect on their mental health and well-being, employment and finances, independence and relationships.

Care Burden

MLD children are entirely dependent and parents' lives are almost exclusively dedicated to their care. The consensus in patient communities is that children are entirely dependent and require 'around the clock' care. In our survey, **6 LI mothers reported time spent on caring as 24 hours per day, 7 days per week; a 2 further Mother's spent around 100 hours per week**. **This was also the case for 50% of fathers and 8 out of 10 patients also received additional care support from professional carers (40%), hospices (70%) and respite care (30%**). In the EJ cohort, Mothers spend an average of 56 hours per week; Father's spent 46 hours per week; professional support was required between 20-45 hours per week (p.75).

Parents in the wider MLD community and our survey have also communicated the physical implications of caring for their child, due to manual handling, including **tendinitis, neck pain, back pain, shoulder pain and hip pain**. Many have also acknowledged the loss of independence due to the demands and intensity of their role as carer and the great impact which their caring role has had on 'normal' life. They report that is difficult to undertake simple things like shopping or have family outings, due to logistical impracticalities and the affected child's relentless care regime.

Damage to Mental Health

Mental health issues are abundant in MLD affected families, who communicate the common feelings of **intense grief, extreme stress, depression, anxiety, panic, isolation, anger, guilt**. This is evident in the constant dialogue between families in the MLD community on social media; in the contact between families and our charity; and is also echoed in the caregiver survey, for example:

The rapid loss of skills can be particularly distressing for the child and the parents: ***"From that age of two to three where he lost his physical ability before his mental faculties was very traumatic for him and for us and physically painful and emotionally upsetting and confusing and distressing for [child] and for us."*** (p.23).

As can the cumulative impact of the situation: ***"In a nutshell, it's destroyed our lives really. It has destroyed our lives completely and utterly. Not just [Name]'s, but ours as well because we've had to watch it and there's really not much we can do really. And probably extended family as well, grandparents. It's not just us, not just me and [Name]. I think grandparents as well. It's destroyed their lives as well, really."***(p.53).

Negative Financial Impact

Parents ability to work is inevitably affected by their situation. Having to forgo their career aspirations is very difficult for parents and leaving work to become a full-time carer dramatically affects their household income. In 75% of surveyed LI families, one parent had to leave employment and for 25% of families this was both parents. 67% of EJ families report that one parents was unable to work and in 33% of families both parents were unable to work. **90% of LI and 100% of EJ affected families were therefore claiming state benefits, including Carer's Allowance, Child Tax Credit, Disability Living Allowance, Employment Support, Housing Benefit, Universal Credit and Working Tax Credit**. Estimated **additional costs of £261,022.80 and £182,636.80 per annum** are incurred outside of direct hospital care for LI and EJ patients respectively (ref. BSC Costs for MLD).

Families also rely upon their wider family for financial help and approach numerous charities, including ArchAngel MLD Trust, to fund to specialist equipment, home adaptations, therapy services and respite care. ArchAngel is also aware of a number of families who appear not to qualify for an NHS Continuing Care package (despite their child requiring care 24 hours a day), due to not meeting standardised assessment criteria which does not cater for the complexities of MLD, which results in significant additional stress. A number of families report to ArchAngel that they have transitioned from 2 average/above average incomes and owning their own home to total dependence on state benefits and Local Authority housing.

Adverse Effect on Relationships

Relationships with partners are dramatically affected by having an MLD affected child and we are aware of numerous irrevocable breakdowns in partnerships and marriages across the wider MLD community, due to all of the repercussions mentioned above. Many survey respondents report "severe marital problems" and one described a challenging dynamic: **"*extreme stress on relationship and marriage but we are bound by total reliance on each other for the care of our family."*** (p.87).

Many known families also report a wide-ranging impact on siblings, including: grief and loss as they witness their sibling lose abilities, suffer and pass away; taking second place to their sibling's medical needs; loss of childhood and adopting a care role. One surveyed family commented on their elder (unaffected) child's experience: "***Worry, guilt, not always being able to go places that they would like, separation from parents when siblings are ill or need care, having to grow up quickly. Majority of the time having to take second place."*** (p.89).

It is apparent that friendships and relationships with wider family are also greatly affected across all of the MLD community and those surveyed. Several parents lamented their child's loss of friends, as other children could no longer relate to or interact with

	their child. Parents also said they frequently saw their own friendships drift away, as parents became increasing isolated due to their responsibilities and friends struggled to understand their situation and/or felt unable to offer physical, emotional or financial support. This further exacerbates mental health issues and indeed all aspects of the care-giver burden compound to result in a profoundly difficult daily existence.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	16% of surveyed parents felt disappointment in their child's diagnostic journey; 74% of surveyed parents felt care was excellent/very good in Specialist centres; 32% of parents had experienced a lack of knowledge in local teams; 16% felt NHS service was slow, which was particularly unhelpful given the fast rate of decline; 5% felt their experience was poor and that they "had to fight for everything".
8. Is there an unmet need for patients with this condition?	**There is a clear unmet need for this technology. There no treatment option only best supportive care. This care is challenging and time intensive in terms of clinical management, which presents a significant burden to the NHS.** Clinicians concur that multiple symptom management, across GI issues, chest infections, secretions and suctioning, dystonia and spasticity, is extremely time intensive and has a huge impact on NHS services (ref. MLD Clinical Meeting). This quote relates to one symptom: ***"MLD is one of the most challenging conditions that dieticians looks after in terms of management and medications have had to be adjusted on a weekly basic to keep some patients nourished".*** The high level of symptom management and intervention is reflected in the caregiver survey: **Hospitalisations** On average LI patients required an average of 2-10 hospital outpatient visits in month period, although for one patient there were in excess of 100 visits (p.68). These patients also had a mean of three hospitalisations (range 1-7) and the mean length of stay on hospital was 15 days (2-33). EJ patients had on average 14 outpatients visits per year, with less hospitalisations, but an average 11-night stay when required. **Medications/Routine Interventions** MLD patients require multiple medications, including: anti-secretion (LI 88%/EJ 100%); anti-seizure (LI 75% / EJ 67%); digestive medications (LI 63% / EJ 100%); muscle relaxants (LI 88% / EJ 100%); pain medication (LI 88% / EJ 100%); other LI 13%. Routine interventions are also common, including: oxygen (LI 13%); enemas (LI 25% / EJ 33%); suctioning (LI 75% / EJ 67%); urinary catheterisation (LI 38% / EJ 33%); brace for scoliosis (EJ 33%). **Surgeries**

	Surgeries carry increased risk to MLD patients and are avoided where possible, however our survey recorded the following unavoidable surgeries: gastrostomy tube (LI 90% / EJ 100%); gall bladder removal (LI 20%); hip dislocation (LI 10%); scoliosis (EJ 33%); tendon severing (LI 10%). Haematopoietic Stem Cell Transplant (HSCT) has been applied to MLD in the past with variable and challenging results. Clinicians report that it has not been carried out in the UK for some time and is no longer considered as appropriate/standard care. **The clinical view is that HSCT is not suitable for LI and EJ patients. Clinicians feel that "gene therapy is a step-change in the management of MLD with no comparator".**
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**The experiences of those untreated patients and those treated with Gene Therapy and are strikingly different.** In our knowledge of over 33 world-wide patients who have received this treatment, this treatment has achieved remarkable results, with many children still asymptomatic at the same age, or having surpassed the age, of when an elder untreated sibling had passed away. A parent of one treated and one untreated LI child said in our survey: ***"It 100% saved his life. That's just the facts of the matter. It's not my opinion. It's the difference between life and death. Certain death and life. And a fit and happy and able and engaged and healthy young boy."*** (p.40) (Treated aged 5, sibling deceased aged 5). The respondents to our UK survey also demonstrate a status which is in distinct contrast to untreated patients across all areas of symptoms and symptom management. *NB. It is important to remember that 66% of EJ Gene Therapy patients already had 'mild' symptoms prior to treatment*: **Mobility** 100% of untreated LI patients are immobile - 100% of LI Gene Therapy patients are able to walk independently; 100% of untreated EJ patients are immobile - 33% of EJ Gene Therapy patients walk independently; 66% are wheelchair users, but can walk with support. **Communication** 80% of untreated LI patients have lost the ability to speak - NO communication issues reported in LI Gene Therapy patients; 100% of untreated EJ patients have lost the ability to speak - 33% of EJ Gene Therapy patients report no communication issues; 66% report some communication issues, but with stability for many years. **Nutrition & Eating** 100% of untreated LI patients are tube fed - NO issues reported in LI Gene Therapy patients; 100% of untreated EJ patients are tube fed - 66% of EJ Gene Therapy patients reported no issues; 33% required assistance due to coordination. No Gene Therapy patients reported any swallowing issues.

	Continence 100% of untreated LI patients are incontinent - NO issues reported in LI Gene Therapy patients; 100% of untreated EJ patients are incontinent - 33% of EJ Gene Therapy patients reported no issues; 66% report incontinence. **Pain & Muscular Skeletal issues** 100% of untreated LI patients have pain and muscular/skeletal issues - NO issues in LI Gene Therapy patients; 100% of untreated EJ patients have pain and muscular issues - 33% of EJ Gene Therapy patients report NO issues; 33% report hip subluxation and mild postural scoliosis due to wheelchair use; 33% report muscle tone issues. **Eyesight & Hearing** 60% of untreated LI patients report issues - NO issues reported in LI Gene Therapy patients; 100% of untreated EJ patients are blind - 66% of EJ Gene Therapy patients report NO issues; 33% wear glasses. **Respiratory Issues** 80% of untreated LI patients report issues - NO issues reported in LI Gene Therapy patients; 100% of untreated EJ patients report issues - NO issues reported in EJ Gene Therapy patients. **Neurological Issues** 88% of untreated LI patients suffer seizures - 66% of LI Gene Therapy patients report no issues; 33% of LI patients report mild peripheral neuropathy; 67% of untreated EJ patients suffer seizures - 33% of EJ Gene Therapy patients report seizure activity post-treatment; 33% report peripheral neuropathy. **Cognition & Impact on Education** 72% of untreated LI patients were unable to attend school - 100% of LI Gene Therapy patients were attending full-time mainstream school. One patient required some assistance with mobility; 100% of untreated EJ patients attend specialist school - 33% of EJ Gene Therapy patients attend full-time mainstream; 66% attend specialist schools. **Hospitalisations** Untreated LI patients had up to 100 outpatients visits per annum and 7 hospitalisations in a 12 month period - one LI Gene Therapy patient had one outpatient visit or hospitalisation; Untreated EJ patients had an average of 14 appointments and 3 hospitalisations - EJ Gene Therapy patients had an average of 3 outpatient visits and no hospitalisations. **Medications & Interventions** 100% of untreated LI patients required multiple medications - NO medications were required by LI Gene Therapy patients;

	100% of untreated EJ required multiple medications - 33% of EJ Gene Therapy patients required anti-secretion medication; 33% of EJ patients required laxatives; 88% of untreated LI required medical interventions – NO interventions were required in LI Gene Therapy patients; 67% of untreated EJ required medical interventions - 33% of EJ Gene Therapy patients required ankle-foot orthoses. **Surgeries** 90% of untreated LI patients required surgeries - No LI Gene Therapy patients required surgery; 100% of untreated EJ patients required surgeries - 33% of EJ Gene Therapy patients elected to have gall bladder removal (as a precautionary measure); 33% of EJ Gene Therapy patients underwent tendon repair. Further positive benefits to families include: 100% of LI Gene Therapy parents continued in employment (one parent affected temporarily during treatment). 66% of EJ Gene Therapy parents were able to continue in employment; No LI Gene Therapy patients required care related to MLD; Only 1 x EJ Gene Therapy patient required additional care support, due to the arrival of a younger sibling. Additional benefits not fully captured by trial data include one EJ Gene Therapy family reporting a marked reduction in previously extreme sensory processing issues: ***"we absolutely feel like we have our life back as a family".*** (p.55/66). **These results indicate a significant reduction in the suffering of patients, the burden on carers and the drain on NHS resources**. With an autosomal recessive inheritance pattern (families have a 1 in 4 chance of an affected child, resulting in many families with multiple affected children), the availability of Gene Therapy would offer the further benefit of enabling these families to make informed reproductive choices. **100% of surveyed LI parents felt that their child's condition was stable and that their expectations of treatment were met; 100% of surveyed EJ parents felt their child's condition was stable, with 66% having expectations of treatment met** (p.65). **We are of the opinion that this treatment is truly transformative.**
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some surveyed parents described difficulties of being in another country for treatment as part of the clinical trial. If gene therapy was approved by NICE patients would not have to travel overseas, which can be an upheaval for some families. 2 parents also commented on the harsh effects of chemotherapy.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Pre-symptomatic Late-Infantile patients would greatly benefit. Symptomatic LI may not likely benefit, due to rapid disease progression in advance of the treatment becoming effective. Mildly symptomatic Early Juvenile patients would greatly benefit. More symptomatic EJ patients may not benefit, due to potential for continued disease progression in advance of the treatment becoming effective. Families with children already affected would be able to make better reproductive choices and have future affected children treated at the earliest opportunity.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The United Nations Convention on the Rights of the Child indicates that “Every child has the right to life“ (Article 6) and “Every Child has the right to the best possible health” (Article 24). We believe that denying children the opportunity of a proven life-saving treatment would demonstrate inequality and inequity.
Other issues	
13. Are there any other issues that you would like the committee to consider?	One-off treatment may carry a premium, however this treatment is potentially curative and the cost is likely comparable to the cost of other authorised life-long therapies which are repeatedly applied to ‘manage’ other rare diseases. NICE should be prepared to be flexible on the requirement for long-term evidence with more novel therapies. **Gene Therapy is a significantly important emerging technology which suggests great potential for application to many other important health problems in the future. Gene Therapy could be routinely performed in existing UK centres where bone marrow transplantation is already carried out.**

NICE National Institute for Health and Care Excellence

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: 1. **MLD patients face immeasurable suffering and certain premature death. There is clear unmet need for treatment.** 2. **MLD patients endure multiple incapacitating symptoms, creating a significant burden to caregivers and resulting in wide-reaching repercussions across relationships, finances, physical and mental health.** 3. **MLD is time intensive in terms of highly specialist clinical management, which presents both challenge and financial burden to the NHS, Dept. for Work & Pensions and Local Authorities.** 4. **The experiences of untreated patients and those treated with Gene Therapy and are strikingly different. GT has demonstrated that it allows children to fully participate in everyday life, achieve an education and attain their full potential.** 5. **Gene Therapy is ground-breaking technology which suggests great potential for application to many other important health problems in the future.**

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MLD Support Association UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	MLD Support Association UK was set up in 2012 by two families with current experience of MLD to bring hope to other families in the fight to eradicate Metachromatic Leukodystrophy (MLD). We aim to provide support to families, personally, through our Website and Facebook group, and at annual Family Conferences and Family Fun days. Funding is by private donations and also supported events such as Marathons, sky-diving, Golf Days, etc. There are six Trustees and we support approximately 45 families.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	MLD Support Association UK has received funding from Orchard Therapeutics for the Development and Maintenance of a National Registry for Patients with Metachromatic Leukodystrophy (MLD). This funding amounted to £7,250. The MPS Society, ArchAngel Trust and MLD Support Association UK has received joint funding of £11,600 to carry out a patient and carer burden Survey.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	I am the parent of a son who has Adult-Onset MLD. He was diagnosed in 1995, and had a Bone Marrow Transplant in 1996. I have, therefore, been dealing with MLD for over 25 years. In that time I helped set up MLD Support Association UK and have supported over 60 families. I believe that this gives me a very broad understanding of all forms of MLD, and the significant problems our families experience. A Study was commissioned by the MPS Society, MLD Support Association UK and ArchAngel Foundation to interrogate the Patient and Carer experience of the Burden of Disease in Metachromatic Leukodystrophy. The report from this research will be uploaded separately. The study consisted of an on-line survey and follow-up in depth interviews. The study was open to those aged 18 years and over, resident in the UK or Republic of Ireland that: • had a confirmed diagnosis of MLD or, • were the parent or carer of a person with a confirmed diagnosis of MLD or, • were a bereaved parent or carer of a person with a confirmed diagnosis of MLD • were able to provide informed consent to participate A total of 24 responses were received, representing 20 families (two families had two children with MLD, one family had three children with MLD) and completed the on-line survey. From this group, six parents completed the interviews, including the three families with more than one child with MLD, giving a total of ten individuals with MLD.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	You start grieving for your child on the day of diagnosis. The sense of loss and the immense sadness for the life that child will never live to experience. I have been grieving for 25 years and seen my son turn from a bright, university student into someone who has to live in a care home. No parent should be forced to do this if a treatment is available. MLD has a devasting effect on patients of all ages and their families. Families must watch the deterioration and have described MLD as a torture for their child. Parents are under a huge amount of stress with many having to

	leave employment to become full-time carers and carry the burden of physical, mental and social problems that this brings. Relationships with the wider family and friends often break down. Siblings have to take second place to the child with MLD and may become **caregivers** themselves. Children with MLD usually need specialist education from an early age before they become too ill. Those with adult onset MLD are unable to continue in employment or further education as their behaviour and cognitive decline makes it impossible. Families often have to rely on a range of benefits and need to adapt their homes and install specialist equipment to care for their child. Adult patients may need residential care, particularly as their parents age I refer to the report commissioned by the Patient Organisations. One parent with a child with Late-Infantile MLD told us: “From the age of two to three where he lost his physical ability before his mental faculties was very traumatic for him and for us and physically painful and emotionally upsetting and confusing and distressing for [child] and for us. It was terrible to watch him.” Some parents mentioned the occurrence of vomiting. In the on-line survey, one patient was described as experiencing vomiting and diarrhoea 10—15 times a day in the final stages of MLD. The effect of caring for a child with MLD is devastating. Not only is the child suffering, but so is the entire family: “In a nutshell, it’s destroyed our lives really. It has destroyed our lives completely and utterly. Not just [Name]'s, but ours as well because we've had to watch it and there's really not much we can do really. And probably extended family as well, grandparents. It's not just us, not just me and [Name]. I think grandparents as well. It's destroyed their lives as well, really.” “She's been tortured, basically. She is. That's what the disease is doing to her. It’s torturing her little body. And we had to sit and watch that. We have to sit and watch it. And other than cuddling her and giving her meds, there’s just nothing we can… And I’d swap places with her.” At our Clinical Meeting it was agreed that pain is a major concern in the management of patients with MLD and can be difficult to treat due to its multifactorial nature. The main causes include gastrointestinal (GI) problems, reflux, dystonia, muscle spasms / spasticity, skeletal pain and neuropathic pain. One of the parents commented: “She would take a long time to fall asleep and she would cry a lot as well. She was in pain, but it wasn’t obvious where she might be in pain.” Not being able to find out why your child is in pain, nor being able to relieve it is very common in MLD.

	Severe dystonia, spasticity, hip dislocation and spinal problems are commonly seen in MLD. Parents reported periods of prolonged pain due to hip dislocations. Clinical teams confirmed that excruciating pain can occur while a hip is dislocating. Once a hip is fully dislocated it generally does not cause any further problems. Sleep deprivation is also extremely common in parents caring 24/7 for their children. One parent told us "We really struggle with the whole sleep situation. We've started the process about nine months ago to actually get some extra care in overnight. On a personal level for myself and my husband, there's a lot of sleep deprivation goes on in this house. She can be up twice through the night or she could be up 20 times through the night. It really just depends how well she's feeling, really. Isolation is also a major problem: "Good friends have now become acquaintances, people are unsure what to say/do so they avoid you and your family My whole time is dedicated to my MLD child and [I] feel bad that I miss out with the other children. Loss of friends My daughter has lost friendships" There is also good evidence that siblings suffer, both from being put second to the child with MLD, and seeing them lose their abilities: "The impact on [patient's] brother has been enormous. He was his stem cell donor and feels immense guilt because it was [patient] who got ill and not him. He shies away from caring from [patient], even after 25 years and still carries the feelings of guilt. "[Brother] has grieved for the loss of [name's] skills. He openly talks about how he wishes [name] could play with him again and how he is sad that he can't walk or talk. [Brother] has been witness to [name] being in a lot of pain with dystonia and with violent sickness." An adult-onset patient was able to read up about the disease, which was immensely harrowing for him. His words the night before his transplant were: "**I would rather die of anything than MLD."**
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is currently no treatment available in the UK, so supportive and palliative care until death is the only option at the moment. For adult-onset MLD there is the possibility of stem cell transplant as long as the sufferer is only mildly symptomatic. However, this procedure is dangerous and gruelling and the risk of acute or chronic graft-vs-host disease is very high. Also, this procedure is not recommended for Late-Infantile or Juvenile MLD as outcomes in

	the USA have proved very unsatisfactory. The view from the MLD clinical meeting held on 20 October 2020, was that head to head, gene therapy was the superior treatment and there was no comparison with HSCT. A copy of the summary of this meeting is being uploaded separately.
8. Is there an unmet need for patients with this condition?	All cases of untreated MLD are life-limiting. The time from diagnosis to death depends upon the type of MLD, with Late-Infantile MLD having the shortest time until death around the age of 5, and adult-onset having a long, lingering death often 20 years or more after diagnosis. It was acknowledged at our Clinical Meeting “that many patients are primarily managed by a neurologist and that some are not known to the IMD teams. It was felt that good coordination of care across IMD, neurology and palliative care was essential in managing both new and existing patients” It was also reported by the clinicians that GI problems are extremely prevalent in non-treated LI and EJ patients and they persistently struggle to gain weight and to thrive. They are complex, multi-systemic, and extremely hard to treat. One centre reported that MLD is one of the most challenging conditions that their dietician looks after in terms of management and that medications have had to be adjusted on a weekly basis to keep some patients adequately nourished. As MLD is considered a “rare disease”, until recently there has been little research and no treatment option, thus no hope for families. This means that once one child is diagnosed, and a sibling is subsequently diagnosed, then the parents are just waiting for the younger child to develop symptoms and watch both their children suffer and die. Many parents also cite the fact that most health professionals have no experience or knowledge of MLD. Local hospitals often lack experience of MLD which can make it difficult to obtain appropriate care. The service was described as slow in many cases, which is a concern given how quickly MLD can progress. One parent commented: “Nursing staff did not understand illness e.g. when [patient] had a seizure and was admitted to hospital - the staff said that [patient] was uncooperative as [patient] did not wash or eat food put in front of [patient] or speak - all of which [patient] was actually unable to do!" Also, with no treatment available it means there are significant implications for the families reproductive plans.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	One parent, who took part in our survey and interview, who has two children with LI MLD, one child untreated and one child treated with Gene Therapy makes an agonising comparison: “I feel like in our case it’s very black and white. At [treated child]’s age now [untreated child] was fully paralysed and we were waiting for the day when he wouldn’t be with us anymore. Now he’s endured for another two years, and he’s still with us now. But [treated child] would be identical to that if he hadn’t got the treatment. It saved his life 100%. That’s just facts of the matter. **It’s not my opinion. It’s the difference between life and death**. Certain death and life. And a fit and happy and able and engaged and healthy young boy**. And [untreated child]’s life has been a torture, an absolute torture. “** Another family commented: “we absolutely feel like we have our life back as a family, and we can go to restaurants. We can take [Name] on holiday. We can take her to swimming school. We can take her to the art gallery We can take her anywhere we know that she’s not going to have a sensory overload” A family with two treated children commented: It’s all completely normal. When you compare the [treated children] to [untreated child], [untreated child] was completely hospital dependent at this point, and then obviously, passed away. So, to compare that to the [treated children] is completely different” A family who had a child treated pre-symptomatically after diagnosis of an older sibling: ‘‘It's actually… I don't want to say healed. I don’t know what the right word is. Is that actually the right word, healed, or? I don't know. Regenerated.“… He’s keeping up with his peers. He’s in Year 5 and just loving life and making the absolute most of every day. He’s not really a rocket scientist. He did what he needs to, but he’s far happier playing and playing football. And he goes to school for the social side of it, I think is what I’m trying to say. But he keeps up. He is hitting what he is supposed to be doing. As long as he continues to hit what is the average and he doesn't struggle with anything, I can't ask for anything more, really.” Another parent commented: “And we’re absolutely delighted with the changes and the improvements that we’ve seen, and 100% feel like the treatment was the right thing to do for her.” Gene therapy has given the children treated the chance of a normal life. Several of the families whose children were treated with gene therapy have older children with MLD who they have seen deteriorate or die. A trustee of one of the patient organisations that support MLD described the impact of gene therapy:

	"I can hand on heart say that the gene therapy results that I have seen have been truly remarkable, and that I've seen children and their elder siblings who have been in the most horrific state, and then passed away. To see the children who are their younger siblings, who've been through gene therapy, and who have no sign of the disease, who are running around as perfect children, like every other child of their age, going to school, taking part in sports, winning medals, and just living life to the fullest. The difference that I've seen in those children and those remarkable results, and the most horrendous, devastating impact, in terms of loss of all ability, and then loss of life, and loss of meaning of life and meaning of being alive for their parents. There is no comparison. " As far as we aware, this is a one-time treatment which will transform the lives of sufferers of MLD and I refer to pages 11 – 13 of the Survey of the Burden of Care in MLD to show the vast differences between children who received no treatment and children who received Gene Therapy in Milan.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	One parent described the difficulties of being treated in Italy when her older child with MLD was nearing the end of life. The separation from family and language barrier were difficult to deal with. "Treatment took place in another country. Language barrier, no family/friend support network, financial implications and logistics were issues. We also had a poorly MLD elder sibling with us who missed out on treatment." One parent with two children with MLD, one treated and one untreated commented: "**There are none from our experience. It is a lifesaving therapy. My 2 boys and the difference between them are living proof of this."** A family commented on how critical it is to have treatment before there are too many symptoms: "I wish my [child] had received treatment sooner so she would have stabilised at a less damaging point." The conditioning regime was also mentioned: "I think chemotherapy is always going to be difficult for anybody to go through. The side effects of the chemotherapy weren't pleasant. I think that seeing your child go through horrible side effects, I think actually has more of a traumatic impact for the parents than the child. …The chemo. But I think that's just a fairly standard side effect of chemo, so I wouldn't say that it was particular to this treatment. I would just say that the chemo isn't great.''

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Clinicial discussion on potential eligible patients included: LI patient should be pre-symptomatic. EJ patients either pre-symptomatic or with early symptoms (These may include gait issues, walking without assistance, behaviour issues (ADHD), memory issues and school performance). Our research shows that the children treated when pre-symptomatic were leading normal lives, attending mainstream schools and with no mobility problems. Children with EJ MLD treated when mildly symptomatic has less beneficial outcomes: “No longer able to walk, unable to feed herself, academically younger, immature for age, unable to perform normal everyday tasks we take for granted.”
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	MLD is multi-ethnic and does not seem to have major differences between populations. Inequality may be seen if there is an inability to travel to designated centres. As it stands at the moment, we see that this treatment is not available for sufferers of Late Juvenile MLD or Adult-Onset MLD. As these are later in presenting and less aggressive, there would be a much larger window of opportunity to provide Gene Therapy to younger siblings whilst they are pre-symptomatic. This should be considered for the future.

Other issues	
13. Are there any other issues that you would like the committee to consider?	We understand that a trial of Intrathecal Enzyme Replacement Therapy (ERT) for treating MLD is about to commence. However, this treatment will need to be continuous and will require many hospital visits, potentially weekly or fortnightly. Intrathecal catheterisation can have some problems, including shifting of the catheter out of the intrathecal space and also headaches. As this trial has not yet started in the UK it will be many years before it may become available to all patients. It would appear from all the evidence we have gathered that pre-symptomatic treatment is the best option, hence there is a need to lobby more for Newborn screening in the UK.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Without treatment MLD is a life-limiting illness in all cases
- No treatment is currently available in the UK
- After Gene Therapy the suffering of the children and the burden of care on families is greatly reduced
- In the later stages of MLD the pain and suffering is almost unbearable.
- The cost of on-going care provided by the NHS is huge, and after Gene Therapy would be greatly reduced

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	The MPS Society

3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MPS Society is the only organisation in the UK that provides support to patients diagnosed with one of 25 MPS or related lysosomal disorder. The organisation supports over 1,500 children, adults and families. The MPS Society was established in 1982, with the aim of providing support, information, and advice to affected individuals and families. The MPS Society does not receive any statutory funding in England, therefore the MPS Society relies upon a rolling programme of grant applications to Trusts and Foundations, together with monies raised by members and the public through fundraising. The MPS Society receive grants from pharmaceutical companies to support the different activities it provides.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	The MPS Society has received funding from Orchard therapeutics for the following - Advocacy, COVID-19 emergency funding, digital communications, MPS III information resource (support for publication of MPS III study). This has totalled £14,000 The MPS Society, ArchAngel MLD Trust and MLD Support Association UK have received joint funding of £11,600 to carry out a patient & carer burden survey.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Three MLD patient groups (The MPS Society, MLD Support Association UK and ArkAngel MLD Trust) collaborated to carry out a survey on Metachromatic leukodystrophy (MLD) burden of disease on patients and care givers. The survey was circulated across the UK and Eire and incorporated both an online survey and individual patient interviews. 24 individual surveys across 20 families were received with 10 patient interviews taking place also (this represents over 50% of known patients to the collective patient groups with 88% of responses being from England). Areas covered included symptoms, disease progression, burden of illness and treatment. The survey was conducted by Rare Disease Research Partners (RDRP) (1) A clinical round table, was convened to share the findings from the survey and to gather clinical experiences and opinions in the management and potential future treatment for MLD (2) From the data collected through the survey and individual parent / carer interviews, we were able to review best supportive care costs outside of the NHS and compare these against costs for a similar neurodegenerative condition (3) (1) MLD groups & Rare Disease Research Partners. Patient and carer burden of MLD – UK & EIRE survey. Unpublished report. December 2020 (2) Metachromatic Leukodystrophy clinical meeting. Unpublished report. October 2020 (3) Case studies of the cost burden for untreated late infantile and early juvenile patients outside of direct hospital care. Unpublished report. November 2020 (4) Judith Beschle et al. *Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy*, 2020, PMID 32910272
Living with the condition	
6. What is it like to live with the condition? What do carers	Metachromatic Leuckodystrophy (MLD) is a heterogeneous, multi systemic progressive disorder with different clinical subtypes depicted by onset of symptoms. • (LI) Late infantile (symptom onset at less than 30 months of age)

experience when caring for someone with the condition?	• (EJ) Early juvenile (symptom onset between 30 months and 6 years of age) • (LJ) Late juvenile (symptom onset between 7 and 16 years of age) • Adult onset (symptom onset at 17 years of age or older) (1) In England, we estimate that there are approximately 28 patients known to the HSS clinical centres. Approximately 19 are paediatric patients with six LI and EJ patients treated with OTL-200. As the expected treatment, groups are LI and EJ the focus of this report is on these two groups. LI MLD is rapidly progressive multifactorial condition, which results in a total loss of all functions. First symptoms usually occur within the first few years of life with a mean age of 1.5 years with death occurring at the mean age of 6.3 years. Inability to start walking is usually the first symptoms reported by parents / carers. Most individuals meet all their learning and talking milestones but this is rapidly lost within 1 year from diagnosis. Average time from first symptoms to diagnosis is 11months. **(1, page 11).** LI patients will loose all their mobility and become fully wheelchair dependent / bed bound within a matter of a few years. *"So, when we moved in, she was still able to climb up the stairs and get herself into bed. Obviously, she wasn't walking, but she was crawling well enough to be able to crawl up and down stairs and climb in and out of bed. And by the time we moved out six months later, she was in a hospital bed, completely bedbound" (***six-month period following diagnosis) (1, page 22)*** "and then by the Christmas he wasn't doing any of it. So no crawling, no talking, no walking, no eating. We had three months and it all just went really quickly."(**1, page 22)*** Individuals also suffer terribly with their muscles, joints and bones with over 80% of individuals suffering from dystonia and spasticity / hypertonia. Other issues include hypotonia and hip subluxation **(1 page 27).** Loss of cognitive function is progressive. Nearly all individual were able to talk and were cognitively aware pre diagnosis with 70% of patients losing the ability to speak by diagnosis **(1, page 25 & 26).** Clinical opinion was that cognitive function appeared to be the last symptom area that individuals lost even after communication was lost **(2, page 2).** This may account for 60 % of individuals reported to suffer from anxiety / panic attacks, as they are unable to communicate their thoughts and feelings **(1, page 29).** Other neurological reported symptoms include; seizures, issues with temperature regulation, sleep disturbance and uncontrolled crying. Chest and respiratory issues are also dominant features of MLD, with many individuals having repeated chest infections, excess secretions, aspirating and requiring frequent suctioning. 100% of patients require enteral feeding (nasogastric, gastrostomy, jejunostomy tubes) due to failure to thrive and weight loss caused by issues including gut dystonia, feed intolerance, and autonomic problems .. Gastrointestinal problems are

	complex to treat and manage with one clinical centre reporting, *"MLD is one of the most challenging conditions that their dietician looks after in terms of management and that medications have had to be adjusted on a weekly basis to keep some patients adequately nourished"* ***(2 page 4)*****.** Diarrhoea and constipation is also highly prevalent with carers reporting having to change their child 10-15 times a day. *A parents of a EJ patient reported "She was sick all the time, constantly morning, noon, night, through the night. She was just constantly sick. We'd get up in the morning and there will be a pile of washing from the night before. And it could have been just been a couple of towels [?] and we'd been lucky to catch it or it could have been the whole bedding and pyjamas and duvets and everything."* ***(1, page 51)*** Pain was an area that was widely reported by both parent / carers and clinical experts. It was felt that causes of pain were multi factorial and could be attributed to dystonia, gut failure, neuropathic or skeletal issues such as hip subluxation or scoliosis **(2, page 4)** *"He gets more and more agitated, and more and more tired, we get more dystonia, and the more dystonia we get, the more it goes into something where he's closer to a seizure"* ***(1, page 22)*** *"painful for him. And then the second one dislocated, and that was, again, another long two or three months of pain before that one came out."* ***(1, page 22)*** The onset of disease in EJ patients appears later with first symptoms reported at the mean age of 5.3 years with a mean length of 7 months until diagnosis **(1, page 12).** EJ patients experience the same symptoms as described for LI, however, their decline is more long and protracted with them remaining in a static stage for long periods of time before further deterioration occurs. Unlike LI, EJ patients usually meet all their developmental (walking, talking and learning) milestone **(1, page 45-47)** First symptoms reported by parent / carers, was the loss of fine and gross motor skills with individuals becoming clumsy, tripping and falling and dropping thing frequently. *""…the first symptoms we felt were related to MLD were I guess around about the age three, she started tripping up quite a lot, and it was just passed off as being a little bit clumsy."* *"…around the age of four, I started to notice that [child would] get really frustrated with things like trying to pull up a zipper or put a lid on a pen. And so, at that point, I had [child] checked out."* ***(1, page 54)*** *"It was very quick, within a couple of months. Certainly, within three months of having a CT scan, she'd stopped walking"* ***(1, page 44)***

	Speech and communication issues are apparent for most patients by the time of diagnosis with dysathria and dysphasia widely seen before loss of all verbal communications **(1, page 47)** **Some patients have used eye communication aid to support dialogue and interactions but this appears to be short lived "** *I think it became apparent quite quickly, within six months, that she didn't have that control anymore. I would say about six months; she couldn't really use it anymore."* ***(1, page 47)*** Cognitive function also declines over time with individuals becoming, more disengaged with activities and academia. *"She was forever making lists. And she was quite a bright academic little girl.She just wasn't interested anymore. She wasn't interested in her reading anymore and she absolutely devoured books. She loved them. There was definitely a marked change in that as well."* ***(1, page 46)*** However, decline in cognitive awareness as with LI patients seems to take place after many of the other skills are lost and individuals are aware of what is happening to them. One parent described this as *"Yes, because she would constantly make comments about, I just don't know what's happening, or my stupid legs, or my stupid hands. She absolutely explained what it was. "* ***(1, page 55)*** Behavioural changes have been under reported in EJ as a first symptom. Parents and carers have observed behavioural changes before diagnosis and this was verified in discussions with clinical experts who described behaviours similar to ADHD and ASD were observed in clinics (**2, page 4)** *"[Reception] just felt she was being difficult and naughty. She was constantly being told off for things that they'd asked her not to do. And scribbled on people's works, scribbling on the wall. She'd been told not to touch something and she touched the paint pots and she did just various things. And they would constantly be coming out and telling me, she's done this and we've asked her not to. She'd always been pretty good in terms of her behaviour."* ***(1, page 49)*** *"When I picked her up, the nursery teacher and the classroom assistant both came to the door and their words were… I can still remember them. You need to get a doctor to have a really good look at her because she is not the little girl that left here six months ago."* ***(1, page 49)*** Loss of sight and blindness was reported in 100% of cases "she *doesn't look at you anymore when you're talking. She used to follow you around the room. Or if you were stood in a corner of the room and you talk, she would look that way. Her eyes would move that way. But her eyes just didn't seem to focus on anything anymore."* ***(1, page 48)***

	Sleep disturbance increases as the disease progresses with many families needing extra night time care to manage this *"[We really struggle with the whole sleep situation. We've started the process about nine months ago to actually get some extra care in overnight. On a personal level for myself and my husband, there's a lot of sleep deprivation goes on in this house. She can be up twice through the night or she could be up 20 times through the night. It really just depends how well she's feeling, really."* ***(1, page 50)*** The burden on parents /carer and wider family is all encompassing. Clinical experts also commented that managing symptoms effectively is very challenging as it is not always clear what the causes are. Patients usually have multiple visits to hospital with many experiencing prolonged admissions **(1 page 68)** Advanced care planning and end of life care is required from an early stage with all patients needing 24/7 care. This burden firstly falls to parents/ carers with many having to give up work, becoming full time carers, experiencing loss of income and financial hardship. Mothers of LI patients reported providing 100 hrs or more of care a week with fathers providing 70 hrs of care a week **(1, page 74)** As the disease progresses many require additional nursing care, overnight care and respite to manage and function day to day. **(1)** Best supportive care costs outside of the NHS are substantial with estimated costs being between £200,000 and £400,000 per year **(3).** Family life and making memories becomes a challenge as intensive nursing care and support takes over. Nearly all LI patients were only able to attend some form of education for a short time with reduced hours. 72% were receiving some level of home schooling at home**.(1, page 25)** EJ patients were attending SEN schools with some on a reduced timetable **(1, page 73)** Many have to have their home adapted and require many specialist pieces of equipment to manage symptoms and meet the individuals nursing care requirements. Many parent / carers have ongoing battles and guilt on whether to treat or symptom management. *"I was like, it feels like there's something going on there. And I suppose a lot of the time we have that conversation with the professionals of, is this worth investigating? And I hate that word, is it worth? Or do we want to put [name] through an investigation? And nine times out of ten, if it's something like an operation, or anything like that, then we do sit down and think, is this sensible, could this be the right decision for him, or do we just need to manage it how best we can manage it? And at the moment we are managing it."****(1, page 33)***

	Activities of everyday life (ADL) were severely impacted with many parent / carers reporting that family and social lives were affected and there were feelings of isolation not being able to go out. The impact on their health and wellbeing included areas of physical pain (back and neck pain, stress, anxiety, grief and depression were expressed **(1, pages 86-89)** For families where there are other siblings the burden on both the parents and siblings should not be overlooked. Many siblings experience a huge amount of guilt, loss, processing their own thoughts and feelings and being relied on as carers **(1, page 89)** *"Worry, guilt, not always able to go places that they would like, separation from parents when siblings are ill or need care, have to grow up quickly. Majority of time have to take 2nd place."* *"Extraneous grief and stress on our daughter aged 8 now, over the course of her life."* *"My daughter and stepdaughter were and still are extremely close. But instead of being equals as they were when they were younger and both mobile, my stepdaughter now has taken on a more caring mothering role."* *"Older sibling upset and angry- has counselling to help understand feelings."* One parents description of how the disease has affected their child life *"And [names]'s life has been a torture, an absolute torture. "* ***(1, page 34)*** LJ and Adult MLD patients experience many of the symptoms described above but a slower rate of progression. Patients however, tend to exhibit neuro cognitive issues first with physical decline and other symptoms appearing later.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Pathways to diagnosis has been challenging and not an easy journey for many. Most experienced significant delays from first symptoms to finally receiving a diagnosis. For one parent this resulted in their child not being eligible for gene therapy **(1, page 76)** *"I think pre-diagnosis I was made to feel like I was going crazy, that I need to just except my child was delayed and 'celebrate who he is'. I didn't feel listened to and it took me to use my concerns around mental health to get a neurologist to look at [name]."(**1, page 77)***

	"When trying to find diagnosis- dismissive to the point of being negligent. We went to a private consultant who then investigated under NHS- this was thorough and allied to diagnosis." ***(1, page 77)*** Although most parents have said that the care they receive from their specialist centres has been good, the care received via their local hospital and care teams has been variable with concerns about the lack of knowledge and ability to assess and provide the right care. This is concerning as many patients are in the palliative care stages and are unlikely to travel to their specialist centre so rely on local hospitals to manage symptoms. *"Care since diagnosis has generally been good. Our team is amazing, and I really value and respect them. Generally, the care we have had in hospital has been really good."* ***(1, page 77)*** *"Over 7 years of problematic care due to inexperience of local teams."* (***1, page 77)*** *"I would say the times which have caused the most stress have been when coming to hospital via A&E and things are not always acted on effectively, leaving [name] in pain."* ***(1, page 77)*** The only disease modifying treatment for MLD is currently hematopoietic stem cell transplant (HSCT). This is not a treatment that is used in practice for LI ad EJ patients and is only offered to adult patients. Outcome data for LI and EJ has not been great and clinical opinion was that HSCT was not a suitable treatment for LI and EJ patients **(2, page 5)** A comparative study of 12 EJ patients treated with HSCT compared to 35 non treated EJ patients was conducted in Germany. The conclusion of the study was that HSCT could accelerate disease progression faster than in non-treated patients and could prompt disease progression. (Judith Beschle et al) *(4)*
8. Is there an unmet need for patients with this condition?	Currently access to gene therapy is not available and the only option for LI and EJ patients is palliative care, which is substandard due to the complexities of managing the condition and the inexperience of local hospitals to manage symptoms.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Gene therapy is a step change in the treatment of LI and EJ patients. It is the one chance of providing patients and carers a normal life without pain, rapid progression of symptoms and the early death of patients. The extent of correction appears to be much improved with many of the major symptoms experienced by non treated patients not being seen in the treated populations. For example; gastrointestinal, vision, pain, chest & respiratory problem and neurological issues are all positively affected or not present in most cases. Cognitive function appears normal to near normal in LI patients and only mild symptoms in EJ patients. All children are attending either mainstream or a SEN school full time. All individuals are only

	attending routine follow up appointments with no hospital stays. The carer burden is reduced to normal parameters when caring for a child in most cases and Q of L and access to the community and socialisation back to normal also **(1, pages 35-41 and pages)** LI patients treated pre-symptomatically have largely shown no progression in their disease and have maintained this for a number of years. One patient does have some peripheral neuropathy, sensory issues but this is mild **(1, page 37)** A few patients have mild issues with walking with one requiring splints. The other is deemed not related to MLD and is caused by a twisted thigh bone (**1, pages 35-36)** *"I feel like in our case it's very black and white. At [treated child]'s age now [untreated child] was fully paralysed and we were waiting for the day when he wouldn't be with us anymore. Now he's endured for another two years, and he's still with us now. But [treated child] would be identical to that if he hadn't got the treatment. It saved his life 100%. That's just facts of the matter. It's not my opinion. It's the difference between life and death. Certain death and life. And a fit and happy and able and engaged and healthy young boy. And [untreated child]'s life has been a torture, an absolute torture. "* ***(1, page 40)*** Expectations of treatment had been met 100% by all parent / carers interviewed *"For [child] to live as normal life and healthy for as long as possible so far this is being achieved."* ***(1, page40)*** *"giving him the miracle of life that he is now living."* EJ patients treated with early symptoms (issues with walking but still mobile) have also shown to have a positive effect and patients have remained stable post treatment. Some regression has been seen during the time of treatment delivery and the treatment becoming effective. Clinical opinion concurred that treatment was likely to take approximately 6 months to become effective and therefore during this time some deterioration could happen. **(3, page 5)** However, in all UK cases, symptoms have stabilised and have not progressed. For the patient who was asymptomatic no disease progression or symptoms were reported (**1, page 63)** *"He's keeping up with his peers. He's in Year 5 and just loving life and making the absolute most of every day. He's not really a rocket scientist. He did what he needs to, but he's far happier playing and playing football. And he goes to school for the social side of it, I think is what I'm trying to say. But he keeps up. He is hitting what he is supposed to be doing. As long as he continues to hit what is the average and he doesn't struggle with anything, I can't ask for anything more, really."* ***(1, page 58)*** *"…the behavioural issues started to disappear quite quickly, and we just noticed even at the point where we'd first come out of the hospital in Milan, that [name] was much calmer, and wasn't going into these crying meltdowns* ***(1 page 63)***

	Parents have also described some cognitive decline during the time for treatment to become effective but this has now stabilised in all cases **(1 page 64)** *"He's just loving life and making the absolute most of every day."* *"And we're absolutely delighted with the changes and the improvements that we've seen, and I won't pretend that [Name] doesn't need a significant amount of help because of their physical disabilities, but physical disabilities can be managed with equipment and with understanding the right techniques and the right support. And we feel that that is very manageable. We would have a much harder time, and we feel like [Name] would have a much harder life if she had more cognitive impairment. 100% feel like the treatment was the right thing to do for her." **(1, page 66)*** Clinicians felt that gene therapy was a step change in the management of MLD with no comparator. The outcomes have been extremely positive and superior to HSCT, which is not considered to be, a viable option for LI and EJ patients **(3, page 5)** A trustee of one of the patient groups said *"I can hand on heart say that the gene therapy results that I have seen have been truly remarkable, and that I've seen children and their elder siblings who have been in the most horrific state, and then passed away. To see the children who are their younger siblings, who've been through gene therapy, and who have no sign of the disease, who are running around as perfect children, like every other child of their age, going to school, taking part in sports, winning medals, and just living life to the fullest **(1, page 12)***
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Disadvantages documented through the patient caregiver experience of treatment survey 2020 were • the challenges of access the treatment in another country and having to relocate. This would not be a major issue if treatment was provided in England • That some progression of MLD can occur while the treatment is taking effect. • The side effects of the chemotherapy before treatment were difficult for both patients and families **(1, page 14)** *"As with any Bone Marrow Transplant, there is a window when the treatment is taking effect when disease progression can occur in SOME children, triggered by the chemotherapy regimen. Nevertheless, subsequent disease stability can still significantly alter the natural course of the disease for the better." **(1, page 66)*** *"… she didn't like the fact that [chemotherapy] did make her incontinent. That wasn't great. The chemo **(1, page 62)*** "*There are none from our experience. It is a lifesaving therapy. My 2 boys and the difference between them are living proof of this." **(1, page 41)***

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As explained above the treatment as we understand it, is intended for LI patients (pre symptomatic) and EJ patients (early symptoms or pre symptomatic)
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None known**
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • This treatment is a step change in treating LI and EJ forms of MLD and is far superior to HSCT, not currently used in this population. • The treatment has been well tolerated and has been shown to prevent onset of disease or stabilise and stop further progression • Treatment outcomes have been shown to be effective in the long-term with no regression reported in the UK population • Outcomes have benefited both patients and parent / carers greatly and have improved Q of L • Treated patients and parent/carers are able to contribute to society and are no longer a cost burden to the NHS and social care providers

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Paul Gissen**
2. Name of organisation	**UCL Great Ormond Street Institute of Child Health**

3. Job title or position	
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This treatment is aimed to stop progression of the disease.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Minimal or no neurological progression of disease from 6 months after treatment is a clinically significant treatment response.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is a high unmet need for patients with MLD. Clinical trial demonstrated efficacy of gene and stem cell therapy in late infantile and early juvenile forms of MLD. There is no approved therapy for these patients as bone marrow transplant would not be offered.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Current treatment for late infantile and early juvenile forms of MLD on the NHS is palliative and symptom care.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	According to the clinical guidelines allogeneic bone marrow transplant is not offered in these forms of MLD because of poor outcomes. There are no other specific clinical guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	MLD is a lysosomal storage disorder and all patients can be referred to the clinical centres with expertise in lysosomal storage disorders. However, because no treatment is currently available not all patients are referred and some are managed locally, where symptom management is possible. We have been able to refer some patients for compassionate use treatment with gene therapy to Milan as this was not possible to receive in the UK. Hence we look after 4 patients with MLD who have received gene therapy in Milan.
• What impact would the technology have on the current pathway of care?	The pathway will be better defined and more patients will be treated in the LSD centres that also have bone marrow transplant centre on site.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This treatment is not currently available on the NHS. Bone marrow transplantation is only available for the late juvenile form of MLD. There is already a close collaboration between LSD centres and bone marrow transplant (BMT) units because many of the LSDs are already treated by bone marrow transplant. Hence, there are already pathways in place that will allow this treatment to be delivered in a seamless manner.

• How does healthcare resource use differ between the technology and current care?	The patients will be initially managed by both LSD and BMT clinicians before they are discharged by the BMT units. I suspect that because the technology will arrest disease progression the patients will not require intensive symptome care management. For example this will minimise the need for gastrostomy surgery and respiratory support.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Autologous bone marrow transplant with the gene therapy should be performed in an experienced bone marrow transplant unit with LSD clinicians support. This will only be possible in a specialist paediatric centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Paediatric centres with BMT and LSD units are already well set up to manage prior, during and after therapy administration. There will be a need for some training specific to gene therapy administration.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes absolutely. The results of the trials are supportive of this statement.
• Do you expect the technology to increase length of life more than current care?	Yes. The treatment with gene therapy significantly improves patients prognosis.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Any patient with MLD.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	This is a once off therapy which need to be delivered in a specialist centre. It is not currently offered. This treatment needs to be delivered as soon as possible after the diagnosis in order to achieve the best results. The patient will need to undergo prolonged admission to the BMT unit.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment is a one-off administration and cannot be stopped. There will need to be adherence to the inclusion criteria proposed, i.e. pre-symptomatic patients with late infantile form and early symptomatic with early juvenile forms of the disease. Thorough neurological assements including brain MRI scans and nerve conduction studies will be required.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes it is possible that some of the improvements in the quality of life of patients and families are not included in QALY calculations.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes. Currently, there are no disease modifying treatments offered to these groups of MLD patients. Gene therapy will offer such hope for the families.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes as explained above. Because of the complete lack of disease modifying therapies.
• Does the use of the technology address any particular unmet need of the patient population?	Yes the lack of therapies.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The treatment side effects are related to the bone marrow conditioning. This will render patients temporarily immunosuppressed and will require a period of inpatient stay in an isolation.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Stabilisation in patients mobility and cognitive functioning. Yes they were measured in trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	The trial showed significant improvement in the clinical outcomes compared with the real world data.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	This is an ultra rare disease.
22b. Consider whether these issues are different from issues with current care and why.	no
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Gene therapy for MLD is an innovative treatment.
- It offers a step change in management of late infantile and early juvenile MLD
- The first disease modifying therapy.
- Pathways of care already exist but will be better utilised.
- This therapy will need to be delivered in a specialist Paediatric BMT and LSD centres.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Simon Jones**
2. Name of organisation	**Manchester University NHS foundation trust**

3. Job title or position	**Consultant Paediatric inherited metabolic disease**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Libmeldy is only licensed in the treatment of children with specific types of MLD and before clinical manifestations have emerged. The aim of treatment is to prevent the emergence of clinically significant neurological signs of MLD.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Prevention of disabling neurological signs of the dosease
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is no other current standard of care therapy in this disease which is uniformly fatal in children with the late infantile and early juvenile forms.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	There are no good treatment options, previously some early juvenile patients were offered allogeneic bone marrow transplantation but this was known to be inadequate and no-one in the UK has had this therapy since Libmeldy became available.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical guidelines for the management of MLD are in the process of being written
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Palliative care for untreated patients is delivered variably by paeds neurologists, palliative care specialists, LSD services and local paediatricians. No treatment choice differences of opinion are known to me.
• What impact would the technology have on the current pathway of care?	This would transform the outcomes for those eligible, who are clearly the minority of children diagnosed with MLD.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This therapy is new to the NHS but expertise exists in other ex vivo stem cell gene therapies for lysosomal disorders and the NHS is uniquely placed to deliver this therapy in a well structured national system.

• How does healthcare resource use differ between the technology and current care?	It would be expected that treated patients would not require the supportive care and palliative care currently needed by patients
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist hospital which can offer metabolic autologous ex vivo stem cell gene therapy
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Mainly the coordination of care
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Dramatically – potentially even to normal lengths

• Do you expect the technology to increase health-related quality of life more than current care?	Dramatically – potentially even to normal lengths
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per the SMPC
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Referral to a specialist centre and early diagnosis more critical. Newborn screening would be the ideal way to make this diagnosis now in the era of this therapy

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As per the label. Specialist MDT assessment to determine eligibility is critical. Newborn screening would be the only way to deliver this option to all potential patients with this disease in the UK.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	As QOL has not been extensively and prospectively studied in this disease it is likely that the models underestimate all the benefits of the technology and the reduction in QOL seen with the disease
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes- highly innovative

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, from no good treatment options and certain death to an almost normal health state (based on longest term data)
• Does the use of the technology address any particular unmet need of the patient population?	As above
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the acute stages post autologous transplant the immediate risks relate to conditioning and risks of infection. It would be expected that from 1 year post HSCT there would be no residual risk from the procedure.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	No – this therapy has only been used in 1 site in Milan.
• If not, how could the results be extrapolated to the UK setting?	UK outcome data likely to be at least as good as the clinical trials as 1) The label states the population eligible to be very similar (more strict in fact) than clinical trials 2) UK site has been externally assessed by Orchard as approved for delivery of this technology and has extensive experience in allogeneic transplantation in lysosomal disorders and also in other ex vivo stem cell gene therapies like this one.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Survival and gross motor outcomes - yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	yes
• Are there any adverse effects that were not apparent in clinical trials	Not as yet

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. How do data on real-world experience compare with the trial data?	No experience as yet- all data in trials
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Only a minority of patients with MLD in the Uk will be eligible for this therapy – entirely depending on when they are diagnosed in the course of their disease. This will generate some very challenging inequality and the only way to address this and improve outcomes more generally is to implement newborn screening for MLD in the UK.
22b. Consider whether these issues are different from issues with current care and why.	n/a

Key messages
23. In up to 5 bullet points, please summarise the key messages of your statement. • Uniformly fatal disease in early onset cases • Transformative therapy with excellent long-term outcomes • NHS in England well placed to deliver this therapy and has centralised diagnosis and care of these children • NHS in England has expert LSD transplant centres and currently selected as one of 5 approved European centres •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Rahul Raman Singh**
2. Name of organisation	**Guys and St.Thomas' Hospital NHS Foundation Trust**

3. Job title or position	**Consultant Paediatric Neurologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve motor function To improve cognitive function To halt motor progression To halt cognitive decline To improve quality of life of patient and carers To increase the activity of ARSA To Improve MRI score TO improve NCV index
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	As above, to halt progression of symptoms in pre-symptomatic children
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a great unmet need in this group as of now, treatment for these conditions are predominantly supportive and symptomatic. There is a need for a definitive treatment

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Supportive and Symptomatic Treatment
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Nothing existing in the UK
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Nothing well defined, very scattered pathway of care. NHSE is in process of developing centres dedicated to IWMD service to unify the pathway across the UK. We have been in touch with our European colleagues regarding pathway of care and it seems there is no uniformity of care. We are aiming to provide care for this group of patients under the umbrella of IWMD (Inherited White Matter Disease) with dedicated Paediatrics and Adult centres across the UK.
• What impact would the technology have on the current pathway of care?	It will have direct impact on the patient's clinical condition, and this will have numerous effect of other aspects of care. This treatment if made available in the UK, patient will not go to international centres to get these therapies. This will also open up pathways for other emerging therapies.
11. Will the technology be used (or is it already used) in	I am not aware if this technology LV-based HSC-GT being used in paediatric centres in the UK

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There is use of the technology, this is the future of many emerging therapies, I am not aware in current care how many centres in the UK are using this technology for therapeutic purposes. I am aware of few trials of this technology. May be I am not answering the question, but the bottom line is this is going to be the future.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Well supported Tertiary centres only.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training to effectively and safely deliver the treatment, Training to effectively monitor the treatment and short, medium and long term outcomes (good/adverse both).
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	Yes, I expect it to help patients who would otherwise die.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Pre-symptomatic patients Late Infantile MLD- More effective, Children with Early Juvenile MLD who have diagnosis made before they have symptoms (as a part of family screening)- More effective. It would eb less effective in symptomatic children, with low neurocognitive scores at the onset of treatment or rapidly progressive MLDs.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	This is going to be an advanced therapy, will require a proper setup to screen, deliver, a proper referral pathways and monitoring of this technology. There are different arms of the technology and this would need meticulous care as with other chemotherapy (Myeloablative therapies).

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, this would need to be defined very appropriately, This is going to be one off treatment so long term monitoring would be crucial.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
17. Do you consider the technology to be innovative in	Yes

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Myeloablative therapies related secondary effects will have its own morbidities. The published data has not got the long term follow up, but this needs to be observed.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Trending
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Halt in progression of symptoms (motor/cognition)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	We don't have that long term data, but within the reported timeframe it seems the outcome was good.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not reported yet
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Trial data looks good and the real world experience is that MLD is a life limiting disease
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes, it is autosomal recessive conditions and more common among families where marriages are common among close relatives. We need to be sensitive regarding their beliefs in these forms of therapies. In Jehovah Witness group, there might be some issues with HSCT- this has to eb explored
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Definitive therapy
- Futuristic/Trending Technology
- Right Treatment Centre
- Right Monitoring
- Improve Quality of Life

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

…Rahul Singh,19/02/2021 ……

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nicola Elson**
2. Are you (please tick all that apply):	☐ a patient with the condition? √ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Archangel MLD Trust, MPS Society and MLD Support Association UK
4. Did your nominating organisation submit a submission?	√ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	√ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	√ I have personal experience of the condition √ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	Up until the age of five our eldest child's development had been normal, however several months after her fifth birthday, it was very apparent to myself as her parent that she was having difficulties. She started having behavioural issues, was inattentive and could not remember things of follow instructions. Initially we felt it was related to a change in school. We pleaded with the school for help, but we were dismissed as neurotic, nervous parents. She suffered terribly during those first few months at school, she was quite often made an example of and punished for things she no longer understood as wrong or dangerous. Quite often she could not recall what she had done that had led to the punishment and was often coming home from school distressed and upset. With no help from the school being forthcoming we took the decision to reduce her hours at school. Approximately six weeks later, no further forward with any help or support from the school and attitudes unchanged, we felt she was no longer welcome as part of the school community and took the decision to removed her completely. During the same period, from around

	the age of five, we attended the GP surgery several times with issues as described above and which we now understand were caused by disease progression. We were also concerned about her hearing and whether this was the cause of her concentration issues and her ability to perform tasks. At this time, she also started having absences which we were told were 'Petit mal' and something she would likely grow out of. She had also had wetting accidents which were totally out of character for my daughter who had been dry since the age of two. Around four months after we first presented to the GP with these initial issues, it became increasingly clear that there was something very wrong happening, she was not the same little girl and had regressed to a much younger age. We discussed our concerns with the GP and there was talk of referring her for physiological assessment. It was only when her Nursery Teacher from her previous educational setting spoke to the GP personally, seconding our concern, that a CT scan was arranged. It took approximately six months from raising our initial concerns to the CT scan on the 20th June 2014. It was a further two weeks before she had an MRI and bloodwork (carried out at Manchester Children's hospital) and three days later we were given the Metachromatic Leukodystrophy diagnosis. During that time, we had tried so very hard to be heard, all to no avail, it was a very frustrating and extremely upsetting experience. One which leaves us consumed with guilt for not making ourselves heard sooner and potentially giving her a second chance at life. Around a month after my daughter's diagnosis, we received the devastating news that my middle child, three and a half years old at that time, was also affected by the condition. We were then given website details for charities who support families affected by MLD and advised to contact them, there was no emotional or counselling support offered from the NHS at this juncture. In terms of the impact this diagnosis has had on our family, it has destroyed our lives. The distress, heartbreak, utter devastation and guilt are unquantifiable and have affected not only our immediate family but also our extended family and friends.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have	Our home is filled with equipment such as oxygen machines, feeding pumps, suction machines, hospital beds, wheelchairs and hoist systems. We have had to make costly renovations in order to make the house accessible, including a reasonable sized extension, installation of a through floor lift and we have had a wet room fitted. Other expenses include personal care items, wheelchair adapted car, the travel costs incurred as a result of numerous hospital visits and we find washing machines rarely last more than 18 months because of the volume of washing we have. When well enough my daughter attends a special needs school (mornings only) where she has her own one-to-one carer. Once a happy, bright, fun loving

had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	little girl she is no longer able to respond or interact with anybody. Just two weeks after the MRI she had gait issues, within three months she had completely lost the ability to walk and three months after this she had spoken her last words. Six months from the point of diagnosis to hearing her voice for the last time. Now she is tube fed, suffers seizures, she is unable to sit or hold her head up independently and has lost her vision. She requires oxygen, a cocktail of medications to make her comfortable and round the clock care. On average she has 3 to 4 hospital stays a year, of between 5 and 10 days at a time and either myself or my husband will stay with her to provide care. With two other children and a husband who works full time this is always difficult to co-ordinate. I am my daughter's full-time carer. In addition to this, we have carers for four hours a day who help me get her up and put her to bed. We have also been awarded fifty hours of overnight care per week, however due to the rural location of where we live this has impacted on recruitment, meaning there is nobody fulfilling this role at present. Consequently, my husband and I take turns in meeting her nursing and physical needs throughout the night. Sleep deprivation is a huge problem and impacts every aspect of our lives, we are constantly exhausted, irritable and mentally fatigued. We also receive three hours of respite care every two or three weeks, this is provided by hospice staff in our home. Her needs mean that every trip out or visit needs to be planned right down to the smallest detail, even a small walk needs to be organised and arranged. This has also impacted the lives of her siblings as impromptu trips to the park or seaside cannot happen, even inviting their friends into our home can cause difficulties. Doing things together as a family is virtually impossible as there are only a limited number of accessible places we can visit. All aspects of our lives are centred around the needs of our daughter and what is in her best interests. I am no longer able to work as my daughter's condition means she needs a full-time carer. I suffer with back problems due to handling and moving, life is generally very stressful and can lead to bouts of depression and anxiety. Possibly the most difficult thing as a parent, is to watch the torture and suffering of your child, knowing there is nothing you can do to prevent it. My middle child still has some fond memories of his older sister before she became poorly. These memories mean there are times when his sister's deterioration affects his wellbeing. During these times he will spend his pocket money buying her gifts and speak about the time 'when she was walking and talking'. Although I feel there is some element of survivor's guilt, I believe the strongest

	emotions are those of loss and sorrow. In the past we have had to self-fund counselling for our middle child, after much research we were unable to find any opportunities through charities or the NHS. Although my son has also been diagnosed with Metachromatic Leukodystrophy, his main concern is and always has been the comfort and needs of his sister. Other than the clinical evaluations in Italy and the occasional hospital visits, there is nothing notable about his condition and he does not consider himself different or unique in comparison to his friends. Quite simply, he is one of the boys' and that is a huge comfort to us as his parents. However, it is fair to say that I will always be on high alert for any indication that my son is struggling with any aspect of life.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	My middle child was pre symptomatic on diagnosis and was assessed for a stem cell transplant. Although he met the requirements for the transplant there were huge uncertainties over the benefits of this treatment and the feedback from doctors and other medical professionals was that this treatment would not prevent peripheral nerve damage and it was not uncommon for individuals to need multiple transplants. The treatment would also not prevent further disease progression and could in fact cause other problems. Balancing this against the huge risks of the procedure, we decided against this treatment. Care in respect of palliative care and the level of physiotherapy offered is poor. As the condition progresses so too does the level of medication, equipment and support required, this is not always forthcoming and quite often we have to challenge what has been offered.
11. Is there an unmet need for patients with this condition?	Quality Physiotherapy is of paramount importance with regard to alleviating/preventing serious muscle and bone complications. I personally do not feel this aspect of care is understood particularly well and physiotherapy should be included as part of the daily routine of the individual's palliative care. I believe a clinical hub/centre of excellence would be beneficial. Currently children are treated far and wide across the county seen by many doctors and consultants. Having a team of experts in the condition

	who could meet regularly to share information, improve understanding of the condition, discuss best course of action with regard to symptom management and palliative treatments and produce publications of clinical guidelines for the condition would be invaluable.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends	My middle child had Gene Therapy treatment in December 2014, he was four years old and pre-symptomatic having been diagnosed after his older sibling. Now six years post-transplant he is a typical ten-year-old who continues to thrive. He is in mainstream school and completing the same work to the same standard as his peers, taking part in school sports day and school plays. He is an avid reader and particularly enjoys Percy Jackson and Harry Potter books. He enjoys spending time with friends at school, Cubs, other social events and makes connections with others easily. He plays football and has taken up karate. He loves the great outdoors and is a keen cyclist, a strong swimmer and likes a ramble in the countryside. He is compassionate and caring and has stepped into the role of young carer without hesitation. He is fiercely protective of his older sibling. At present he continues to return to Italy twice a year for clinical assessment as part of the clinical trial for the treatment. He does not require any medication; he does not require any equipment or adaptions and he has one annual appointment to see his consultant here in the UK. My son is fully aware he has Metachromatic Leukodystrophy and Gene Therapy was treatment for the condition. He understands that he is part of a clinical trial and the reason he returns to Italy twice a year for clinical evaluation. He has witnessed first-hand the devastation and destruction this disease unleashes, just six short months after diagnosis at the age of six, his older sister was no longer able to do any of these activities and my son does not take for granted the fact he can. He celebrates his Gene Therapy re-birthday every year, he makes the most of every opportunity he is offered, he lives in the moment and has a passion for life that not many will understand.

and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	It is my understanding that Gene Therapy treatment is far easier for the patient than stem cell Transplant. Conditioning and chemotherapy are less rigorous and the nature of the treatment means less anti-rejection medication is required after transplant. By far the biggest issue for our family was the location and distance. Struggling with the recent diagnosis of our two children we had to embark on a daunting journey to Italy. We neither understood or spoke the language, our accommodation was a hotel room, we were away from family, friends and other support groups at a time when we needed them most. I cannot emphasis enough how traumatic this factor was for our family. Arriving on foreign soil with a suitcase and two young vulnerable children was extremely frightening. If we had been able to access the treatment in this country a significant amount challenges and stress would have been avoided.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are	Overall, my son tolerated the treatment well and the few memories he has of the time are not negative. His condition is stable and he continues to engage in all things ten-year-old boys do without limitation. Other than his clinical assessments in Italy, he sees his paediatric consultant in the UK once a year. He is fit and healthy and other than for a flu vaccine, I cannot recall the last time he needed to see the GP. The side effects were standard chemotherapy related issues, dry mottled skin, raised levels of toxins in the liver, hair loss and mucositis. They were all short-term problems that were resolved relatively quickly with no long-term impact. We were advised there was further, very slight, white matter damage after the 3-month post-transplant MRI, which was not unexpected. A further side effect is the likelihood of fertility issues in the future.

there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	The biggest disadvantage of the treatment was the fact we had to travel abroad, away from our support network with two vulnerable children. My eldest child who was not eligible for treatment, progressed significantly while in Italy. One parent had to travel back with her on more than one occasion for appointments with consultants and Doctors in the UK. There were obvious cost implications in having to do this, flights, taxi's, etc. I also feel it is relevant to mention that these months spent away from home were the last ones before my eldest child lost the ability to walk and talk, she should have been able to spend this time with family and friends making memories. The distress of these irretrievable lost few months caused upset across our wider family.
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	It is my understanding that it can take between 12 to 18 months for the ARSA enzyme production to reach levels so as to become effective. Also, the conditioning treatment and general stresses of lengthy hospital stays can speed up disease progression meaning patients who will benefit most are pre symptomatic or mildly symptomatic.
Equality	
16. Are there any potential equality issues that should be taken into account when	Treatment should be available to all individuals who meet the criteria regardless of age at onset/form of Metachromatic Leukodystrophy (Infantile, Juvenile, Adult).

considering this condition and the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	
Key messages	

18. In up to 5 bullet points, please summarise the key messages of your statement:

- Gene Therapy is a far superior treatment in comparison to the current Stem Cell transplant and is lifesaving if given in a timely manner.
- The Gene Therapy treatment is far less invasive and conditioning much gentler than that of Stem Cell transplant.
- Traveling abroad with vulnerable children away from family, friends and support networks at a time when they are needed most is not ideal.
- The cost of palliative care is immense, not only for the families but for the NHS also.
- Creating a Clinical hub/Centre of Excellence to support families living with Metachromatic Leukodystrophy would be hugely beneficial.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	**Georgina Morton**
2. Are you (please tick all that apply):	☐ a patient with the condition? **X** a carer of a patient with the condition? **X** a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	ArchAngel MLD Trust; The MPS Society; MLD Support Association UK.

4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	**X** I have personal experience of the condition **X** I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: **X** I am drawing on others' experiences. Please specify how this information was gathered: As the parent of an Early Juvenile MLD patient who received Gene Therapy for MLD, our family are connected to over 400 MLD families worldwide and closely connected to 33 other families from around the world who also received Gene Therapy for MLD. This has afforded a unique insight into the advantages/disadvantages of the treatment over a 10-year period and the experiences of many families with multiple affected children, who can directly compare treated and untreated siblings.

	As Chairperson of ArchAngel MLD Trust, I am also connected to 38 UK families/44 patients (including deceased). This has enabled myself and other Trustees to develop many close relationships and an in-depth knowledge of the individual struggles and challenges faced by these families, both within and outside of the health service. ArchAngel MLD Trust works closely with The MPS Society and MLD Support Association UK and these three patient organisations have collectively commissioned a caregiver study to increase understanding of the natural history of MLD, its impact and burden on patients and their families and the effects of gene therapy (attached to each organisation's submission). ArchAngel is also spearheading a campaign to have all UK babies tested for MLD at birth, resulting in membership of several international organisations and alliances, which has facilitated further knowledge about the condition from close working relationships with expert clinical colleagues from both the UK and across the globe.
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	My daughter Ava was diagnosed with Early Juvenile MLD in February 2013, at the age of 6 years and 8 months. With hindsight, the first symptoms of MLD were apparent around the age of 3 years (c.2009). However, due to the rarity of the condition and the lack of suspicion/knowledge of local clinicians, the route to diagnosis was not straightforward. Ava met all of her early developmental milestones with ease and was a happy, confident, outgoing child. First signs of the disease were issues with gross motor skills, including frequent trips and lack of confidence with (and avoidance of) playground equipment. Minor balance and coordination issues also appeared at nursery school, for example difficulty skipping during ballet lessons and refusal to put her coat on, at first assumed to be a behavioural issue but actually due to problems with motor planning/coordination. We became worried that Ava may have been showing signs of Arthritis, which her maternal Grandfather has suffered from since teen age. Ava then became increasingly frustrated by inaccuracy in her fine motor skills, getting annoyed by simple things like putting a lid on a pen or pulling up a zipper on her clothes. Concerns were raised with a GP who diagnosed ocular muscle weakness and reassured us that such issues were commonplace at this age/stage of development. Around the same time, Ava began to exhibit high levels of anxiety at home when faced with simple decisions, like selecting an outfit for the day. Inability to make a choice would prompt crying and upset could quickly escalate into hysterical screaming. Ava had never had tantrums as a toddler, so this behaviour was entirely out of character. Episodes became increasingly more frequent and would persist for anything from 20 minutes to several hours. During lengthy episodes, no amount of reasoning, distraction or incentive would make any difference to Ava and she would become physically agitated and incapable of engaging on any level. We would need to place her in her cot for safety until she eventually became exhausted and calmed down. Screaming episodes also began happening outside the home for no apparent reason, including during trips to restaurants, the cinema or the swimming pool. We now understand these episodes to have been triggered by sensory processing issues and exaggerated autonomic responses to noise or other physical sensations, like hunger or cold. Concerns were once again raised with a GP, who made no connection with her motor issues and referred Ava to a psychologist for behavioural problems. Behavioural 'problems' progressively impacted upon family life, with episodes occurring at least every day and up to 10 times each day. Daily routines were upset or abandoned and we were frequently asked to leave venues due to disruption to other

	clients, eventually leading us to avoid most social situations. By this point I was also frequently called home from work to deal with incidents which child carers could not cope with (e.g. hysterical screaming in the changing area after a swimming class) and after going through a succession of nannies, all of whom left due to these unmanageable behavioural episodes, I was forced to leave my employment as a television producer to care for Ava. Ava's elder sister Angelina became increasingly resentful of the constant need to change our plans or miss out on events and activities due to this behaviour, as well as the high level of attention being dedicated towards 'managing' Ava in general. Once Ava began Primary School in September 2011, behavioural issues were not evident during the school day and we attributed this to the extensive effort we had put into employing disciplinary techniques recommended by the psychologist (although with hindsight the calm environment of a very small independent all-girls school was likely a contributor) but episodes of hysteria did continue at home. School PE teachers however did pick up on the disparity between Ava's physical skills and those of her peers – i.e. with hopping, skipping, jumping, throwing, catching - and in March 2012 recommended she undergo an assessment for Dyspraxia. We referred this recommendation to Ava's GP and in May 2012 a 'child development' assessment was carried out. As part of this process, Ava's class teacher completed a questionnaire, in which she described observing Ava to have an occasional tremor in her hands when she went to pick up a pencil or other classroom object. Upon reading this, I also realised that I had noticed a similar tremor, intermittently, at home. Richard had not noticed this, however it became evident with further observation. The assessment concluded that Ava had a mild case of Dyspraxia and that some Occupational Therapy would be of benefit. However, Richard and I were not satisfied with this opinion, particularly in light of the tremor, which we felt implied a serious neurological issue and which was very concerning. The paediatrician reluctantly agreed to refer Ava for an MRI brain scan. The MRI was conducted in October 2011, however results were not forthcoming and we pushed to secure an appointment with the paediatrician. During this appointment we were informed that Ava's MRI revealed an "underdevelopment of myelin", which was "nothing to worry about at this age". We were entirely unconvinced that an abnormal MRI should be dismissed in this way and pushed for further possible explanation of the findings. The paediatrician then agreed to undertake some blood tests, purely as a process of elimination, to reassure us that there was nothing untoward. Blood tests were carried out quickly, however we did not receive any results and repeated attempts to make contact with the referring paediatrician failed. By this point (Feb 2013) we were incredibly anxious and after 12 weeks of silence I visited the paediatrician's office in person, on the off chance that someone would engage with us. Her PA apologised for ignoring our calls "because it was bad news". We were given no explanation and an appointment for 3 days hence. After 3 days of heightened anxiety and intense worry, we attended a short meeting. It began with the doctor handing me a print-out from the internet entitled 'MLD 101' and her informing us that Ava had a condition that she had never heard of called Metachromatic Leukodystrophy. She went on to say that it was a 'life limiting' condition and that Ava would not live to reach teen age. I was immediately devastated and began to cry, however Richard remained calm and asked for the name of the leading expert in this type of disorder, to which the doctor said "sorry, no idea". He asked if there was anyone who could give us further information and she said she would look into it and get back to us. I asked what would happen next and again she said she wasn't sure but would come back to us.

	We went home entirely shell-shocked. I was so distraught that I was barely able to speak, whereas Richard was in a state of total disbelief that we had effectively been given a death sentence for Ava and then sent on our way. He decided to call Great Ormond Street Hospital and managed to secure an appointment with a metabolic consultant there 2 days later. The next 48 hours were incredibly difficult. We decided to say nothing to Ava or Angelina until we had confirmation of the facts from GOSH. So we held our emotions together in front of them and then cried for many hours in private. We also spent the first of many sleepless nights researching the condition. The internet informed us that Ava was missing the ARSA enzyme, without which toxic material called sulfatides would build up and destroy her nervous system. She would lose her ability to walk, to talk, to swallow, to see, to hear; she would develop epilepsy, dementia, an unresponsive state and, after all of this immeasurable suffering, pass away. We learned that with the Late Infantile form of the disease, children rarely survived past the age of 5. Since Ava had met her major milestones of walking and talking, we deduced that she had the Early Juvenile form, which would follow the same trajectory, just at a slower rate and that death in teenage was highly likely. It was truly horrific reading and we were utterly devastated imagining Ava enduring such torture. However, given that Ava was able to run, swim and cycle, this prognosis seemed to bear no relation to the child we saw before us and the more we read, the more we became convinced that a second opinion of this diagnosis from GOSH would reveal a mistake. The metabolic consultant at GOSH confirmed that the diagnosis of MLD was correct. After a physical examination, he remarked how “well preserved” Ava was, but proceeded to inform us that unfortunately there was no treatment available and that we should do everything we could to make Ava comfortable and prepare for her to systematically lose all of her abilities; to make some happy memories whilst we still had the chance. We were incredulous at the prospect of no treatment options and I asked about Bone Marrow Transplant, which I had read about on a US MLD website. The consultant explained that BMT had been carried out on a small number of MLD patients in the UK in the past, but with very poor outcomes, so this treatment was no longer available. Richard asked about clinical trials and we were told “someone is doing something with mice, but that is a long way off and wouldn’t be relevant to Ava”. The consultant also stated that since there was no treatment available, the appointment at GOSH was a ‘one-off’ and that going forwards Ava’s symptoms would be managed by her local hospital. We felt entirely abandoned by the system and couldn’t accept that there was no treatment or even expertise to help Ava. After further research, we did in fact find two applicable clinical trials, one for Enzyme Replacement Therapy (ERT) based in Copenhagen and one for Gene Therapy, based in Milan. We contacted the consultant again to discuss these trials (and establish why they weren’t mentioned previously) were informed that they weren’t mentioned because Ava “did not qualify” to take part. This was entirely inaccurate. Thanks to our acute sense of desperation to do something rather than nothing, we proceeded to refer Ava to these clinical trials ourselves. She passed all motor and cognitive assessments with flying colours and was offered a place on both trials. We chose to pursue Gene Therapy over ERT, as the trial itself was further advanced. 10 children had already been treated, demonstrating evidence of efficacy and no adverse effects. In contrast, the ERT trial was only just commencing and the trial leader explained that at that point the dose of ARSA enzyme was such a small amount that it would be unlikely to affect the disease, although it would be increased in time should the first stage of trial prove successful. Gene therapy was also favourable as it was a one-off treatment with potential to arrest progression of the disease, whereas any approved ERT would be for a life-long regime of regular infusions with potential for ongoing ‘management’ of the condition.

	Despite being incredibly fortunate enough to have Ava diagnosed in time to receive the opportunity of gene therapy, nevertheless our diagnostic experience greatly impacted upon our mental health and we experienced an unrelenting cycle of shock, distress, fear, anxiety, grief and desperation. Richard's ability to work was also greatly affected. We felt that our experience was both appalling and lamentable in equal measure and we were saddened to subsequently learn from the MLD community, through close personal relationships and via ArchAngel, that a bad diagnostic experience is in fact fairly commonplace. For Late Infantile children, diagnosis has tended to be faster, given the failure to meet major developmental milestones. However, many LI and Early Juvenile parents recall being ignored or dismissed as neurotic, often resorting to trips to A&E in a desperate attempt to get a second opinion on worrying symptoms. A number of EJ parents have also received a misdiagnosis, with Cerebral Palsy being a common error, until their children have continued to decline (as opposed to plateauing with CP) and then reconsidered. Many MLD parents continue to lament missed opportunities to enrol their child in Enzyme Replacement or Gene Therapy trials due to delays or failures in the diagnostic process.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school	Although Ava was considered to be only 'mildly' symptomatic, nevertheless our experience of living with MLD prior to Gene Therapy was very challenging and disruptive to family life. Not only did we miss out on many typical activities, it was also impossible for Richard and I to have any time away from the children, as Ava would not tolerate being left with a babysitter or new environments, which would lead to her experiencing panic and inconsolable crying. We also lost one full income when I was forced to leave my employment and Richard's ability to work and earn money were greatly affected post-diagnosis due to his high stress levels, forcing us to downsize our home twice and putting a significant strain on our relationship. The assumed notion of everyone coming together to support us post diagnosis was a fallacy. Other family members and close friends withdrew as they felt unable to cope with the situation or offer us any support. During the time between Ava's diagnosis and commencing gene therapy (13 months) we connected with a number of other MLD families to find support. However hearing about the immense suffering of their affected children and the fact that parents were for the most part full-time carers - consumed by grief, depression and chronic exhaustion, lacking in any quality of life and inevitably experiencing the total breakdown of relationships - only served as a source of trauma rather than comfort. Having read extensively about MLD, we felt that we clearly understood the condition and what horrors would lie ahead for Ava and our family. All of this only increased our stress levels and we both felt that our lives were surreal, out of control and that all of our hopes and plans for the future were in complete limbo. I suffered from terrible insomnia and was haunted by recurrent mental images of burying Ava. In spite of our understanding of MLD by this point, nothing prepared us for the stark reality of meeting MLD children in person for the first time, which affected all 4 of us profoundly. In April 2013 we took Ava to San Raffaele Hospital in Milan to assess her eligibility for gene therapy. In the waiting room were introduced to two families, each of whom had had two Late Infantile MLD affected children; a pre-symptomatic younger sibling diagnosed in time to receive gene therapy and an elder sibling with advanced disease, ineligible for treatment. The untreated siblings were boys aged 3 and 4 from Saudi Arabia and Norway respectively. The 3 year old was lying in a specialist buggy, he was painfully thin and holding his limbs in a state of extreme spasticity. He was unable to speak, but made perpetual groaning noises and appeared to be agitated and in pain. His mother stroked his head and sang gently to him but he appeared unable to focus on anything or to even acknowledge her. The 4 year old child was also lying in a specialist buggy, the back and underneath of which was laden with medical apparatus connected to the child. The boy appeared to be slipping in and out of consciousness and his mother explained that a cocktail of medication

and social life. What is the effect on any siblings?	had that effect on him, particularly medication for severe epilepsy and for gastrointestinal dysfunction. She also said that he could no longer see or hear and required support to breathe. She said that she watched him every minute of the day in anticipation of him passing away. Both parents said that they were separated from their childrens' fathers due to the intense strain of the situation. They were both clearly sleep deprived and unable to hold back tears. They both articulated their unending gratitude for the opportunity of gene therapy and the chance to save their younger child from the same fate as that of their elder child. Afterwards Angelina (then aged 8) asked if they had the same condition as Ava and began to hyperventilate on the realisation that Ava could end up in the same terrible state of suffering. This panic attack was the first of many which would become a regular feature of Angelina's life for years to come. Ava repeatedly changed the subject and refused to engage in any conversation around the hospital or why we were there. Richard and I felt traumatised by seeing such badly afflicted children and imaging Ava in such an appalling state of suffering. We were also worried by Ava's withdrawal and discussed the impact of seeing these children with the trial leader the following day. She told us in no uncertain terms that Ava needed to understand that MLD was a monster and that she would need to fight it with extraordinary strength, determination and bravery. Although Ava successfully passed the clinical assessments, unfortunately the viral vector required to deliver corrected genes was not immediately available. The trial leader advised us that by the time treatment became physically available to Ava (c.6-9 months), in all likelihood her disease would have progressed to the point where the treatment would be unable to help her, due to the delay between administration and effect of the treatment, which as with any bone marrow transplant could take up to 12 months to become fully effective. There followed an incredibly anxious wait of 10 months, during which we were acutely conscious of the need to avoid Ava sustaining any shock to her nervous system (e.g. virus, bang on the head, which researchers felt correlated with periods of rapid disease progression in their experience of studying MLD children over many years), waiting and watching for signs of disease progression, whilst at the same time attempting to carry on life as normal so as not to worry the girls. Richard and I carried intense feelings of stress, fear and paralysis through this period and many other families have described the exact same feelings and worries following diagnosis. We felt incredibly lucky to have the slim hope of gene therapy through this period of heightened anguish. Ava remained stable and received Gene Therapy for MLD in March 2014. We appreciated that there would be few children to compare her with going forwards. The majority of trial subjects were pre-symptomatic Late Infantile, treated at a very young age (around age 1), as opposed to Ava being a mildly symptomatic Early Juvenile patient being treated at the age of 7 (thereby with a much greater accumulation of toxic sulfatides). We also understood that the treatment would not work immediately and that accumulated sulfatides could continue to damage Ava's nervous system. Nevertheless, we were hopeful of a positive outcome, having witnessed very encouraging results in all of the children treated before her. The disease initially carried on attacking Ava's nervous system during the first year post-transplant whilst the treatment was becoming effective. Her balance and coordination continued to deteriorate and she began to require the use of a wheelchair for longer distances, eventually requiring a wheelchair full-time around 18 months post-treatment, as well as help with feeding and dressing herself. Her processing speed and speech also slowed down and it can now be difficult for unfamiliar people to

	understand her. In additional to a wheelchair, she requires specialist seating at home for the shower and toilet. Whilst there is no doubt that having a child in a wheelchair requires some degree of adjustment to our routines and forward planning for some activities outside the home, many aspects of normal family life have in fact been restored. Ava's behavioural issues improved rapidly and within a few months of receiving treatment her lengthy screaming episodes had dramatically reduced and now no longer occur. Ava's disease has been stable now for almost 7 years post-transplant and whilst we are pragmatic about long-term outcomes of experimental treatment, our lives have been utterly transformed for the better by the opportunity of Gene Therapy and the fact that Ava is a joyful, engaged, motivated child, free from pain and enjoying life (see Q.12). We know all of the other trial families and have maintained close friendships with a high number of them. The LI children who were treat at a much younger age than Ava have had remarkable outcomes with many showing no signs of the disease many years after transplant. The difference between them and their untreated siblings, who are either badly afflicted or deceased, is night and day. Pre-symptomatic Early Juveniles remain unaffected; some mildly symptomatic EJ's have experienced similar issues to Ava before also achieving disease stability. The lives of the untreated children we know bear no comparison to Ava's. Almost without exception they have lost the ability to walk, talk, swallow and are doubly incontinent and they endure complex gastro-intestinal issues, painful spasticity and have developed serious muscular skeletal deformities, including chronic scoliosis and hip dislocations. The majority of children have lost the ability to see, hear and communicate their needs. They suffer epilepsy and dementia; most require suctioning and multiple medications, all of which require frequent adjustment in order to cope with rapid disease progression and change. Children struggle to regulate their temperature, sleep and reactions to sensory stimuli. Parents despair over the fact that their children experience near constant pain and it is extremely difficult to ascertain the cause of this and how to make their child comfortable. Children are entirely dependent upon 1-2 adults 24 hours per day and very few children are able to attend school, even with full 2:1 care. The burden on parents is immeasurable. They are without exception sleep deprived and suffer from back/neck/shoulder pain due to the demands of manual handling. The majority have mental health issues due to the stress of watching their child's intense suffering and this is invariably heightened by the impact of loss of income and freedom which come with being a full-time carer. Countless relationships have broken down, as partnerships are unable to survive this considerable strain. Many families also appeal for support for the siblings of their affected child, who suffer their own mental issues including grief and loss for their sibling, loss of normal childhood and the pressure of adopting a carer's role. Whilst the plight of these untreated children and families has been deeply upsetting to witness, the most heart-breaking contrast for us has been with the Early Juvenile friends whom Ava made after her diagnosis. Many of these friends who appeared to be 'the same' as her at the time have now passed away. Of those who continue to endure, the majority have become totally incapacitated, tube fed, catheterised, unresponsive and frequently hospitalised. The parents of these children are invariably suffering chronic depression and some have expressed the fact that they have no reason for living other than taking care of their child. One of the most disturbing things I have ever witnessed has been the desperation of 2 families who found their child's suffering so unbearable that they chose to withdraw all medication and nutrition in order to expedite death.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	I am not aware of any current alternative treatments. A UK trial for Enzyme Replacement Therapy commenced in December 2020 and this treatment is many years from becoming available, if and when the research returns favourable results. Bone marrow transplant is not an option in the UK and although this is performed in the US, outcomes seen in families with whom I am closely connected are very poor. Some children have continued to experience further disease progression to the point of being unresponsive. For those who have fared better, they still have a number of debilitating complications, including a high level of physical and mental disability and/or chronic Graft Versus Host Disease, requiring frequent hospital admissions and crisis management. Treatment in the UK comprises 'best supportive care' and, despite the tireless efforts of specialist medical teams, it is evident that MLD is one of the most challenging and time intensive conditions to manage. Parents and clinicians alike report that this is due to the catastrophic level of damage inflicted, the number of different areas sustaining damage and a relentless onslaught of progression and change. At ArchAngel MLD Trust, we frequently supply specialist equipment to families as a matter of urgency as NHS supply timeframes mean that equipment is often redundant by the time it arrives. We experienced a distinct lack of support from both the metabolic consultant whom we initially saw at GOSH and a local paediatrician who repeatedly failed to engage with Ava, due to her own admission of lack of experience with MLD. Once Ava was accepted for treatment in Milan, the highly respected medical team there found it very difficult to engage with any UK clinician both before and after Gene Therapy was administered. I was effectively managing Ava's healthcare and was forced into making repeated complaints to the Central London CCG in order to have someone take responsibility for Ava's care in the UK. Fortunately, after making another direct approach to GOSH in 2016, a new metabolic consultant was assigned to Ava and from that point she has received excellent support from this specialist centre. We have continued to experience a lack of engagement from local teams, although this is slowly improving. Failures to support Ava in the UK have been excused by the statement "you left the NHS and had Ava treated abroad". Local therapists have also repeatedly cited lack of experience with MLD as a problem in managing her disabilities, however therapists with experience of neuro-disability continue to manage Ava's needs very effectively. Whilst it is apparent that our difficulties have arisen from the mistakes, misapprehensions or inexperience of certain individuals, I do believe our very unfortunate experiences could have been avoided entirely if this treatment had been approved and was available as routine at one of the UK's specialist centres. Other families we know are generally very satisfied with care they receive from specialist centres, although some also experience lack of knowledge in local teams as we have done. Many families experience frustration with the slowness of NHS services, particularly in relation to the supply of specialist equipment. By the time items are procured, assessments are out of date and recommendations are redundant. For this reason ArchAngel supplies a good deal of specialist equipment, including bespoke wheelchairs, sleep systems and positioning aids, to families on fast turnaround.
11. Is there an unmet need for patients with this condition?	There is clearly an unmet need for this treatment due to the severity of the condition, the rapid speed of deterioration and the lack of any alternative treatment option.

Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	This treatment has demonstrated a clear ability to alter the natural course of the disease and dramatically improve the outcomes of those who have received treatment. I know all of the other trial families and have maintained close friendships with the majority of them. The LI children who were treated at a much younger age than Ava have had remarkable outcomes. Many showing no signs of the disease many years after transplant. The comparison between them and their untreated siblings, who are either badly afflicted or deceased, is night and day – for example the 2nd child to be treated has just celebrated his 10th birthday and is entirely symptom free, whereas his affected sibling passed away at the age of 4. Many of the treated LI children have deceased siblings, whilst they themselves can walk independently and have no communication issues; they have no issues with eating or continence; none of them experience pain or have muscular-skeletal issues; they have no problems with eyesight or hearing; no sensory issues; and require no medication. All of the children who are of school age attend full-time mainstream schools. Many families have deceased MLD children and unequivocally describe Gene Therapy for MLD as miraculous and life-saving. Even though she was treated at the age of 7 and her prognosis was less certain, post-transplant Ava has consistently produced around 10 times the standard amount of the previously missing ARSA enzyme and her brain MRIs have been entirely unchanged since around 18 months post-transplant. Whilst we remain pragmatic about the long-term effects of the treatment, we are greatly encouraged by the fact that Ava's condition remains stable almost 7 years post-transplant. Assessments in 2019 demonstrated small but important signs of recovery in nerve function in short pathways, for e.g. a 50% increase in eye and ear nerves; and small increases in IQ have been consistently observed over the past few years. The results of regular clinical follow-ups are undoubtably reassuring, however another significant mark of success for us has been in the notable quality of life which Ava has been able to maintain and importantly the positive effect which the opportunity of treatment has had on Ava's psyche and the mental health of all members of our family. Ava is an extremely upbeat and content child who enjoys attending school on a daily basis. She engages in daily physical therapy with enthusiasm and striking determination to improve her abilities. She is unfazed by the fact that she can no longer participate in certain physical activities like cycling or trampolining with her sister and friends and instead focusses on the activities which she loves and can participate in, including baking, crafting, gardening, watching movies and singing. She especially looks forwards to parties and playdates. Ava does still exhibit a degree of atypical sensory reactions (e.g. she can startle easily at sudden noises and can be bothered by bright lights), however her sensory processing issues have altered dramatically and the previously debilitating screaming episodes no longer occur. I am now able to work again and run the ArchAngel charity from home on a full-time basis. Richard is in much better mental health and runs a successful business for around 12 hours per day. As a family we regularly attend venues which were previously off-limits, including cinemas, restaurants, art galleries and swimming pools. We have taken several holidays post-treatment without issues, visiting such diverse locations as Marrakech, The Maldives, Florida, Swiss Alps, Amalfi Coast and Rome. Secondary school transition saw Ava move from a mainstream to special school for practical reasons and she is happily settled in a small school, where she is engaged, greatly enjoys learning and where staff report increasing improvements in memory and concentration. She has many

	friends and is known for her sunny disposition and great sense of humour. She especially loves practical and creative subjects including music and art and eagerly participates in regular trips to museums, libraries, gardens and places of worship. Ava and all of the treated children demonstrate a meaningful quality of life which is worlds away from what their lives would undoubtedly have been without treatment. Gene Therapy for MLD has granted these children a second chance of life and their families the privilege of not only seeing them enjoying life but also the luxury of hope for their futures. This treatment also gives families the confidence to make informed future reproductive choices. It goes without saying that treated children have also removed an otherwise significant burden on health services.
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	Gene Therapy itself is a fairly straightforward one-off procedure, essentially delivered via a standard bone marrow transplant. Ava did not suffer any pain or discomfort from the extraction of cells (a short procedure under general anaesthetic) or reintroduction of cells (a small syringe into a catheter, administered without medication and in less than 20 minutes). Side-effects were only experienced in relation to the chemotherapy which was required before administration of the gene corrected cells. Ava and I stayed in the isolation unit for 56 days and in Milan for a total of 4 months. During this time we felt well supported by clinicians and hospital staff. Ava's father and sister travelled back and forth most weekends, as protocol allowed for Richard and I to swap places for a couple of nights each week to ensure that we spent time with both children. It was our choice to coordinate in this way and we had no issues during his period (or indeed the many subsequent follow-up visits). Many other families chose to relocate their entire immediate family unit, especially those having to coordinate the care of other children and in particular the care of other MLD affected children. All families received good local support from trial organisers, who also funded travel, accommodation and other expenses. ArchAngel MLD Trust also funded accommodation for families whose children received treatment on compassionate grounds, rather than by participating in the clinical trial.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the	Aside from the obvious disadvantage of treatment being administered in another country, the main disadvantage of the treatment is the chemotherapy regimen, which caused Ava to experience some vomiting for 2 days and oral mucositis for around 2 weeks. This meant she was unable to eat orally during this period, although this did not appear to bother her, perhaps as she received adequate nutrition intravenously. She also experienced hair loss and incontinence, which had a long-term effect and which she initially found upsetting. Other families also reported sickness, mucositis, hair loss and incontinence; a number also felt highly anxious throughout the treatment. A small number of children suffered from an infection during the period of reduced immune system, which was particularly stressful, especially for one family in the unusual situation of having 2 children (twins) being treated at the same time, whilst also having an untreated elder sibling at end-of-life stage.

treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	From personal experience of being closely connected to 33 families who have received Gene Therapy, I firmly believe that pre-symptomatic Late Infantile patients and mildly symptomatic Early Juvenile patients would greatly benefit from this treatment. They have all demonstrated an unequivocal difference between unaffected/good quality of life and unimaginable suffering/premature death when compared with their untreated siblings and friends.
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	All children have equal rights to the best possible health. Denying the opportunity of life-saving treatment would demonstrate inequality and inequity.
Other issues	
17. Are there any other issues that you would like the committee to consider?	

Key messages
18. In up to 5 bullet points, please summarise the key messages of your statement: • **MLD causes horrific, unrelenting suffering to the affected children. Management of the symptoms is very challening.** • **MLD causes total devastation and disruption to families, even in the early stages of the disease.** • **There is a clear unmet need for treatment in the UK. Specialist centres would only need experience of standard bone marrow transplant procedures to perform Gene Therapy.** • **Gene Therapy is truly transformative. The quality of life in treated vs untreated children is beyond compare.** • **The positive psychological impact of hope which Gene Therapy gives the child and their family is invaluable.**

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Sophie Thomas**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? X a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	The MPS Society, ArchAngel MLD Trust, Alex, The Leukodystrophy Charity and MLD Support Association UK
4. Did your nominating organisation submit a submission?	X yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it X **I agree with the submission from the MPS Society, I have not seen the others.** other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	X yes (the MPS Society submission)
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	
11. Is there an unmet need for patients with this condition?	
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also	

include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they	

long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	
Equality	
16. Are there any potential equality issues that should be taken into account when	

considering this condition and the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement: • • • • •	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**DR AYESHA ALI**
2. Name of organisation	**NHS ENGLAND**

3. Job title or position	**MEDICAL ADVISOR, HIGHLY SPECIALISED SERVICES**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHSE clinical commissioning policies for the treatment of metachromatic leukodystrophy (MLD)
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	The early part of the pathway of care is not well defined for this patient group given the rarity of the condition. Improving awareness raising and earlier diagnosis will be important in signposting patients to established national clinical centres.

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	This technology will represent a step change in the treatment options for patients with MLD
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	The technology is not routinely commissioned
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be administered through existing commissioning arrangements with assurance from the provider/s on governance, infrastructure, safety and quality arrangements in place to deliver the technology
• How does healthcare resource use differ between the technology and current care?	The technology would provide a significant alternative treatment option for this cohort as current care is supportive in nature

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology would be delivered within a centre that is able to meet the requirements previously described and linked into the national highly specialised service for lysosomal storage disorders
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
10. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England
Equality	

11a. Are there any potential equality issues that should be taken into account when considering this treatment?	Given the mode of inheritance consideration may be needed of a higher incidence in some ethnic groups.
11b. Consider whether these issues are different from issues with current care and why.	These issues are not different from current care.

Thank you for your time.

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Evidence Review Group's Report
OTL-200 for treating metachromatic leukodystrophy

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Authors Matthew Walton, Research Fellow, Centre for Reviews and Dissemination, University of York

Mark Corbett, Research Fellow, Centre for Reviews and Dissemination, University of York

Hollie Melton, Research Fellow, Centre for Reviews and Dissemination, University of York

Lindsay Claxton, Research Fellow, Centre for Reviews and Dissemination, University of York

Melissa Harden, Information Specialist, Centre for Reviews and Dissemination, University of York

Robert Hodgson, Research Fellow, Centre for Reviews and Dissemination, University of York

Mark Simmonds, Senior Research Fellow, Centre for Reviews and Dissemination, University of York

Correspondence to Mark Simmonds, Senior Research Fellow, Centre for Reviews and Dissemination, University of York

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Corbett, Mark Simmonds and Hollie Melton wrote the clinical effectiveness sections of the report. Matthew Walton, Robert Hodgson and Lindsay Claxton wrote the cost effectiveness sections and conducted the ERG economic analyses. Melissa Harden wrote the search strategy sections. Mark Simmonds took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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Table of Contents

Table of Tables

Table of Figures

List of abbreviations

AE	Adverse event
ARSA	arylsulfatase A
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CS	Company submission
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
DQ	Development quotient
EJ	Early juvenile
EMA	European Medicines Agency
eMIT	Eelectronic marketing information tool
EPAR	European Public Assessment Report
ERG	Evidence review group
ES	Early symptomatic
EQ-5D	Euroquol 5 dimensions
GLIA	Global leukodystrophy Initiative
GMFC	Gross motor function classification
GMFM	Gross motor function measure
HSCT	Haematopoietic stem cell transplant
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
IDS	Integrated data set
IPD	Individual participant data
IQ	Intelligence quotient
LI	Late infantile
MAC	Myeloablative conditioning regimen
MLD	Metachromatic leukodystrophy
MRI	Magnetic resonance imaging
NCV	Nerve conduction velocity
NHS	National Health Service
NHx	Natural history
NICE	National Institute for Health and Care Excellence
PBMC	Peripheral blood mononuclear cells

PS	Pre-symptomatic
PSS	Personal Social Services
QALY	Quality adjusted life year
SAE	Serious adverse event
sCMFS	Severe cognitive and motor impairment-free survival
SMAC	Submyeloablative conditioning regimen
sMFS	Severe motor impairment-free survival
SmPC	Summary of product characteristics
VAS	Visual Analogue Scale
VCN	Vector copy number
WHO	World Health Organisation

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report; Evidence Review Group Report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

ID1666	Summary of issue	Report sections
1. Exclusion of HSCT as a comparator treatment in the company submission	• Current standard care is modelled to include only palliative supportive care and does not include HSCT which was a listed comparator in the NICE scope. • Clinical opinion indicates HSCT is sometimes used on the NHS and is a relevant comparator in this appraisal.	2.3.3
2. General limitations and poor quality of the evidence base	• OTL-200 has been tested in only a few patients, with limited follow-up. Limited information on patient baseline and results data were submitted, especially for the untreated cohort.	Section 3 particularly: 3.2.2 and 3.2.4.1
3. Long-term trends in motor function outcomes; potential for long term-decline ion motor function	• OTL-200 is assumed to be curative such that stabilisation of disease is assumed to permanently halt progression of all aspects of the disease. • Whilst medium-term graft stability has been demonstrated in other therapeutics, there are factors unique to all such technologies which may impact the long-term durability of treatment effects. • There is evidence that OTL-200 does not prevent disease progression across all systems equally.	3.2.4.2, 3.2.4.3 and 4.2.7.1
4. Potential decline in ARSA activity	• The ERG noted a decline in ARSA activity in CSF in Late Infantile patients after 24 months. This may be of concern as OTL-200 treatment is intended to increase and maintain ARSA activity.	3.2.4.8 and 4.2.7.1
5. Outcomes in patients receiving cryopreserved formulation	• Very early trial data raise the possibility that poorer outcomes may occur in patients receiving the commercial cryopreserved formulation when compared to the trialled fresh formulation.	3.2.5

6. Full response is equivalent to general population health.	• The model assumes that all manifestations of disease are resolved by OTL-200 and does not account for the impact of myeloablative conditioning. • This is inconsistence with surrogate markers of disease and published evidence on the long-term impact of myeloablative conditioning	4.2.2.4 and Effectiveness of OTL-2004.2.7.1
7. OTL-200 preserves cognitive function	• OTL-200 patients are assumed to retain cognitive function even when gross motor function is lost. • While biologically plausible, evidence on DQ and surrogate markers is far from conclusive.	4.2.2.2 and 4.2.7.1
8. Distinction between stable and unstable partial responders	• The small sample size and limited follow up of the trial evidence make it difficult to discern whether the observed declines in GMFC scores are a result of a delayed treatment effect or indicative of continuous progression. • It is therefore plausible that patients currently considered unstable could subsequently stabilise and equally that patients classified as stable could continue to decline.	4.2.2.4 and 4.2.7.1
9. Sub-populations for decision making	• Reflecting the marketing authorisation of the OTL-200 the modelled population includes three distinct sub populations: i) pre-symptomatic late infantile; pre-symptomatic early juvenile; and, symptomatic (GMFC <2) early juvenile. • Results are currently presented as a combined ICER based on a weighted average of ICERs in each sub-population. • Heterogeneity in cost-effectiveness estimates across the three populations is not captured by considering a single decision for the whole population. • There is considerable uncertainty regarding the size of each population, and it is unclear how the company's approach to estimating these integrates the available epidemiological evidence.	4.2.3.3
10. Potential impact of OTL-200 on diagnosis and screening	• The availability of treatment might alter the diagnostic pathway, particularly if new-born testing becomes routine NHS practice. • This may impact on the effectiveness of OTL-200 and the population eligible for treatment.	4.2.3.4
11. Discounting	• The company base-case uses a non-reference discount rate of 1.5%. • There is significant uncertainty whether the relevant criteria are met, particularly in early symptomatic early juvenile patients.	4.2.6
12. Proportion of full responders	• The company designate patients as full responders based solely on GMFC score and in some cases with minimal follow up.	4.2.7.1

	• The pattern of decline in GMFC observed in several patients is counter to the pattern of treatment response in partial stabilisers hypothesised by the company. • The proportion of full responders and stable partial responders is therefore likely overestimated. • In the ES-EJ sub-population a patient is excluded even though they received treatment and would be otherwise eligible under the marketing authorisation. This exclusion leads to the proportion of stable partial responders being overestimated.	
13. Estimation of progression modifier in unstable patients	• It is not fully clear which data were used to estimate a progression modifier applied to partial responders to OTL-200. • The OSR-TIGET natural history cohort used contained a substantial number of missing data points and it may have been better to consider the rate of transition between GMFC 2 and 6 due to lower levels of missing data. • • A different progression modifier informed by clinical opinion was applied to the ES-EJ sub-population. The justification for this approach is unclear.	4.2.7.1
14. Time spent in GMFC 0	• The modelled time in GMFC 0 is too long and inconsistent with data from the OSR-TIGET natural history study.	4.2.7.2
15. Mortality in functionally stabilised patients	• Patients classified as functionally stabilised (i.e. full responders and stabilised partial responders) are assumed to have life expectancy in line with the general population. • There is limited evidence to inform this assumption and several reasons to expect that these individuals will experience morality rates in excess of those experienced by the general population.	4.2.7.3
16. Use of a non-reference case approach to elicit utility values	• In the absence of existing data on the health-related quality of life (HRQoL) of patients with MLD, the company commissioned an elicitation study to generate health state utilities. The study adopted an approach inconsistent with the preferred methods described in the NICE reference case, and preferable alternatives. The company provided insufficient justification for this deviation. • Elicited utilities reflect only public preferences, not those of patients or caregivers. • Additionally, there are a number of issues with the vignettes used used in the elicitation study and evidence of bias. These flaws manifest in which appeared to correspond poorly to external data sources.	4.2.8.2
17. Application of separate LI utility set	• To reflect the fact cognitive decline is less predictable in patients with EJ MLD separate cognitive impairment sub-states were modelled for PS-EJ and ES-EJ patients. These were not applied in the LI population as	4.2.8.3

	cognitive decline accompanies deterioration of gross motor function in a more consistent way. This approach leads to patients in the LI cohort being assigned a different utility set. • There are significant inconsistencies between the LI and EJ utility set likely due to differences in the vignettes used to describe these health states. • This means patients in essentially the same health state are assigned different utility values depending on whether they are in the LI or EJ sub-population.	
18. Face validity and application of separate cognitive impairment decrements	• The applied utility values make extensive use of negative utility values driven in part by a large and independent effect of cognitive impairment upon the modelled utilities. • There is evidence to suggest significant bias in the elicitation study regarding the impact of cognitive impairment. • More generally, the utility values ascribed to two health states are inconsistent with the lowest utility ascribed to the worst EQ-5D health state as valued by the UK general public. The vast majority of BSC patients [redacted] are ascribed the worst utility for much of their lives.	4.2.8.4
19. Age adjustment of utility values	• Utilities were only adjusted as patients aged in GMFC 0. This means that patients who stabilised in GMFC 1 had a higher utility than those who stabilised in GMFC 0 from approximately age 36 onwards. • Decrements are applied assuming HRQoL peaks at birth (using a utility values derived from adults), and deteriorates from patients' first birthday	4.2.8.5
20. Application of carer decrements	• To reflect the burden on caregivers, utility decrements are applied in health states GMFC 5 and 6. • The ERG is satisfied that care of children with MLD is likely to represent a significant burden on families but considers that the physical and psychological burden of caring for children in the earlier stages of the condition mean it is appropriate to apply caregiver decrements from GMFC 1 onwards.	4.2.8.6
21. Resource use applied in GMFC 0	• The cost-effectiveness analysis includes minimal health state costs in GMFC 0 despite requirements for ongoing monitoring. Additionally, as discussed in relation to Issue 6, GMFC scores may fail to capture other manifestations of the disease. Patients classed as functionally stabilised may therefore continue to experience manifestations of disease resulting in additional costs to the NHS.	4.2.9.2
22. Resource use applied patients with late stage disease	• In GMFC-MLD 6, the company's analysis assumes that 80% of patients are cared for in their home, with the remaining 20% of patients are cared for in hospital or a hospice full time. The company further assumes that hospitalised patients will receive substantial	4.2.9.2

	additional social care provision amounting to 7.2 hours per day 292 days per year. • Clinical advice received by the ERG suggested that residential hospital care for patients with MLD is extremely rare and that typically patients with end stage disease will be cared for in the home. • The application of additional social care costs for patients who are cared for in a hospital or hospice setting is likely to double count care costs as any care needs will be covered by hospital/hospice costs already applied.	
23. Resource use for adults with symptomatic MLD.	• Due to the benefits of OTL-200 many of the patients are likely to survive into adulthood. The company analysis, however, assumes that resource use in adult patients is largely the same as those for children in the equivalent health state. • This may not be reasonable. Consultation with the ERG clinical advisor suggest that it is likely that an adult in health states GMFC-MLD 2 or worse will require some degree of care from social services or institutional care.	4.2.9.2

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The ERG prefers to apply the same distribution of cognitive sub-states in equivalent GMFC states regardless of treatment received;
- The ERG revised the distribution across the three sub-populations in line with available epidemiological evidence;
- The ERG applied discount rate of 3.5% to costs and benefits in line with the NICE reference case.
- The ERG Re-estimated the proportion of responders requiring a minimum of 12 months to establish full response and reclassify any patient as unstable who experienced a decline more than 12 months;
- The ERG applied the same set of progression modifiers to pre-symptomatic and early symptomatic EJ patients:
- The ERG re-estimated time spent GMFC 0 using starting age (as reported in the CS) and data from the OSR-TIGET natural history study;
- The ERG applied as set of SMRs to mortality rates applied in GMFC 0 to 5 to account for the impact of myeloablative conditioning and neuro-disability:
- The ERG preferred to apply the same EJ utility set to all patients and therefore revised the utility set apply in LI patients so it was equivalent to the EJ utility set.

- The ERG removed the cognitive impairment utility decrements applied in the model such that HRQoL is determined only by GMFC score i.e. no independent effect of cognitive impairment:
- The ERG corrected the Age adjustment of utility values so that they were only applied to adults and were applied to all health state no just GMFC 0 as modelled by the company; the application of carer decrement so that they applied from GMFC 1 onwards;
- The ERG revised the health state costs applied in heath state GMFC 6 to assume that patients are cared for in a home setting:
- The ERG revised health state costs applied so that a proportion of adult patients are assumed to be cared for in an institutional setting.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival;
- Stabilising or slowing disease progression;

Overall, the technology is modelled to affect costs due to:

- Its higher unit price than some current treatments:
- The greater administration costs associated with the technology.

The modelling assumptions that have the greatest effect on the ICER are:

- That stabilisation of disease progression is permanent and impacts equally on all aspects of the disease;
- Mortality in patients who achieve disease stabilisation;
- The proportion of patients classified as functionally stabilised particular the proportion which stabilise in the absence of any decline in motor skills (full responders);
- The distribution of health states over which late stabilisers are stabilised in, particularly when revisions are made to model additional mortality and adult care for patients with progressed disease;
- The rate at which future costs and benefits are discounted.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Exclusion of HSCT as a comparator treatment in the company submission

Report section	Section 2.3.3 and 4.2.4.2
Description of issue and why the ERG has identified it as important	HSCT was removed from the CS as a comparator treatment and was not considered in the economic analysis despite it being listed in the NICE scope. The ERG notes that the company's economics advisory board provided testimony that indicated HSCT was used in some patients. Further advice from the ERG's own clinical advisor confirmed the use of HSCT and suggested that there would be some overlap between the patient group eligible for HSCT and those eligible for OTL-200.
What alternative approach has the ERG suggested?	Although the ERG has presented published IPD on HSCT outcomes these are very limited in number and do not relate to the NHS setting. Given the limited data currently available, no alternative analysis is feasible.
What is the expected effect on the cost-effectiveness estimates?	Unknown, evidence on the HSCT is limited, but suggests that in the right patients HSCT is effective at delaying progression of disease and prolonging survival. This will reduce the comparative effectiveness of OTL-200.
What additional evidence or analyses might help to resolve this key issue?	Historic data on HSCT outcomes from NHS patients who would have met the eligibility criteria for OTL-200 treatment would help resolve this issue.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 General limitations of the evidence submitted

Report section	Section 3, particularly: 3.2.2 and 3.2.4.1
Description of issue and why the ERG has identified it as important	OTL-200 has only been fully tested on 35 patients, with very small numbers of patients for each patient type (LI, PS-EJ, or ES-EJ).. No RCT has been performed, with patients compared to an untreated historical cohort and, in a small number of cases, to untreated siblings. Limited patient baseline and results data were submitted, especially for the untreated cohort. Clinical study reports (CSRs) requested by the ERG were not provided by the company. The ERG was therefore unable to properly critique the methods of analysis and unable to compare important baseline characteristics across the OTL-200 and comparator cohorts. Interpretation of the submitted comparative analyses was therefore difficult. While the ERG acknowledges that some of these limitations are inevitable, given the nature and rarity of the condition being assessed, there is nevertheless considerable uncertainty in the accuracy and

	reliability of treatment effect estimates, some of which could have been avoided by a clearer and more comprehensive company submission.
What alternative approach has the ERG suggested?	No alternative approach is possible. Hoverer, the ERG notes that provision of IPD and clinical study reports (both were requested by the ERG) could have resolved some uncertainties in analysing the trial data and evaluating comparisons with untreated patients.
What is the expected effect on the cost-effectiveness estimates?	The limitations of the data mean there is significant uncertainty around key model parameters including the proportion of patients who achieve a full or stabilised partial response as well significant uncertainty regarding the durability of stabilisation, see Issue 3.
What additional evidence or analyses might help to resolve this key issue?	Individual patient results data and CSRs, as noted above, would have been helpful but were not provided.

Issue 3 Long-term trends in motor function outcomes

Report section	3.2.4.2, 3.2.4.3 and 4.2.7.1
Description of issue and why the ERG has identified it as important	In the model it OTL-200 is assumed to be curative such that treatment brings about a permanent halt to the progression of all aspects of the disease. This contributes to the significant QALY gains attributed to OTL-200, and in combination with assumptions relating to utilities and mortality means a substantial portion of OTL-200 patients accrue benefits in line with the general population. Biological plausibility of graft stability is insufficient to justify a permanent treatment effect. While medium-term persistence of engineered HSCs has been demonstrated in other therapeutics, there are factors unique to all such technologies which may impact on the long-term durability of the treatment effect. The mode of action in OTL-200 is itself unique amongst available gene therapies, and issues such as gene silencing and unequal attrition of high VCN cell lines (up to 44%) suggest uncertainties with regards to sustained long-term efficacy. A number of OTL-200 patients who appeared stable over several years later experienced symptom decline. Further, there is evidence that OTL-200 does not prevent disease progression across all systems equally. Continued deterioration of peripheral neuropathy in PS and ES-EJ patients treated with OTL-200 was demonstrated by declines in nerve conduction velocity (NCV). It may therefore be plausible that while motor dysfunction driven by CNS progression is halted, progressive demyelination of the peripheral nerves may lead to motor function decline even in full responders.
What alternative approach has the ERG suggested?	Given the data limitations, no further statistical analysis is possible, other than to identify the potential issue. Uncertainty regarding the validity of stabilisation assumptions means it is appropriate to explore more pessimistic scenarios in which patients

	either experience continuous slow progression of disease or where stabilisation is not permanent for all patients.
What is the expected effect on the cost-effectiveness estimates?	Reducing the period of which patients stabilise acts to increase the ICER. In the most pessimistic scenario explored by the ERG where the average period of stability is reduced to 10 years: • The ICER increases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population, The ICER increase from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	Long-term follow-up data into late childhood or adulthood would be required to resolve this issue.

Issue 4 Potential decline in ARSA activity

Report section	3.2.4.8 and 4.2.7.1
Description of issue and why the ERG has identified it as important	The ERG noted a decline in ARSA activity in CSF in Late Infantile patients after 24 months. This may be of concern as OTL-200 treatment is intended to increase and maintain ARSA activity. Due to lack of follow-up beyond 60 months, and the limited data, it is currently unclear whether this decline will continue, whether it is clinically meaningful, and whether it is correlated with poor motor function outcomes. Follow-up in Early Juvenile patients is currently too limited to determine if the same decline in ARSA activity will occur.
What alternative approach has the ERG suggested?	No alternative analysis is feasible.
What is the expected effect on the cost-effectiveness estimates?	There is uncertainty how ARSA activity relates to stabilisation of disease, however, as highlighted in the European Medicines Agency (EMA) considered it likely that continued efficacy was dependent upon maintaining ARSA activity levels above a certain threshold. Declining ARSA may therefore precursor of disease progression. As discussed in Issue 3 graft failure is likely to increase the ICER substantially.
What additional evidence or analyses might help to resolve this key issue?	Further follow up-data on both ARSA activity and motor function outcomes in the OTL-200 patients is required.

Issue 5 Outcomes in patients receiving cryopreserved formulation

Report section	3.2.5
Description of issue and why the ERG has identified it as important	It is anticipated that a cryopreserved formulation of OTL-200 will be used in practice. All the clinical data used in the economic model relates to use of the fresh form. The cryopreserved formulation has only been used in [redacted] patients, with minimal follow-up available. It is therefore currently unclear whether the cryopreserved formulation will achieve the same treatment effects as the fresh formulation. The ERG identified that some of the patients receiving the cryopreserved formulation had stable or declining ARSA activity in the CSF after 6 months, in contrast to improving ARSA activity over that period in patients receiving the fresh formulation. Due to limited data and follow-up, it is currently unclear whether this represents a genuine difference in CSF ARSA activity between formulations.
What alternative approach has the ERG suggested?	Data are currently too limited for any alternative analyses.
What is the expected effect on the cost-effectiveness estimates?	If cryopreserved formula is less effective this may lead to either fewer patients achieving stabilisation or reduced durability of stabilisation This will act to increase the ICER potentially substantially.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up, with motor function outcome data, is required for the patients receiving the cryopreserved formulation. Six-month and one-year CSF ARSA follow up data for more recently recruited patients would also help.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 6 Full response equivalent to general population health

Report section	4.2.2.4 and Effectiveness of OTL-2004.2.7.1
Description of issue and why the ERG has identified it as important	Patients 'fully responding' to OTL-200 were assumed to lead normal healthy lives in line with the general population. This was reflected in the HRQoL, costs and mortality rates applied in the GMFC 0 health state. The ERG recognises the conceptual and biological rationale for the modelled concept of full response, but has concerns that the focus on GMFC scores may be overly simplistic and fail to capture other manifestations of the disease. Trial evidence suggests some aspects of MLD pathology are treated sub-optimally by OTL-200, with patients continuing to suffer renal tubular acidosis, metabolic acidosis, and hepatobiliary disorders. Importantly, the modelled outcomes do not capture the potential effects of continuing peripheral neuropathy observed in the trial. They also do not account for the long-term effects of myeloablative conditioning, which is required as part of the administration of OTL-

	200, and is associated with significant adverse effects including dental problems, short stature, cognitive deficits, and pulmonary dysfunction. The characterisation of full response as normal general population health, may therefore be inappropriate and may serve to overestimate the benefits of OTL-200.
What alternative approach has the ERG suggested?	Without long-term evidence it is difficult to ascribe a quality of life decrement to account for the impact of these other manifestations of disease and long-term effects of myeloablative conditioning. This should be acknowledged when considering the presented ICERs.
What is the expected effect on the cost-effectiveness estimates?	This will lead to the benefits of OTL-200 being overestimated. The resulting ICER will therefore be underestimated.
What additional evidence or analyses might help to resolve this key issue?	Further follow up of full responders may be informative. Further clinical input on the likely impact of disease manifestations not captured by GMFC and the impact of myeloablative conditioning may help to inform an appropriate utility decrement.

Issue 7 OTL-200 preserves cognitive function

Report section	4.2.2.2 and 4.2.7.1
Description of issue and why the ERG has identified it as important	To reflect the fact the MLD impacts upon cognitive as well motor function, patients in each of the GMFC health states were classified into one of three cognitive function substates: Normal/mild loss of cognition (DQ>70); moderate impairment (70 > DQ > 55); and, severe impairment DQ<55). The distribution of patients across the cognitive sub-states was treatment specific and in the OTL-200 arm of the model it was assumed that loss of gross motor function would not necessarily be accompanied by loss of cognitive function. These assumptions strongly favour OTL-200 due to punitive utility decrements applied in the moderate and severe impairment sub-states. Evidence provided by the company providing a direct comparison of the rate of cognitive decline in patients with the OSR-TIGET natural history cohort is not informative in-terms of justifying differential application of the cognitive sub-states. Evidence on surrogate markers is also far from conclusive. Evidence on CSF ARSA activity in partial responders for example, shows patients did not reach the normal reference range in all patients until at least two years after treatment. This is inconsistent with the company's proposed mode of action of OTL-200.
What alternative approach has the ERG suggested?	Given the uncertain evidence to support the assumption that OTL-200 will have an independent and ostensibly stronger treatment effect upon the brain and wider CNS, cognitive decline should accompany deterioration of motor function and aligning with assumptions made in the BSC arm of the model.

What is the expected effect on the cost-effectiveness estimates?	In a scenario in which the same rates of cognitive function are applied in equivalent GMFC states regardless of treatment received: • The ICER is unchanged in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population, • The ICER increase from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	Current evidence cognitive decline is limited to 3 years. Longer-term evidence may support assumptions that cognitive function is retained. A conditional analysis of DQ by motor function using current evidence could also potentially be informative.

Issue 8 Distinction between stable and unstable partial responders

Report section	4.2.2.4 and 4.2.7.1
Description of issue and why the ERG has identified it as important	Patients classified as partial responders were assumed to either stabilise following a period of decline or continue to experience continuous slow progression of disease. The small sample size and limited follow up of the trial evidence make it difficult to discern whether the observed declines in GMFC scores are a result of a delayed treatment effect or indicative of continuous progression. Current biological understanding would suggest stabilisation of disease relatively quickly after treatment; however, this is subject to considerable uncertainty. As such it is plausible that patients currently considered unstable could subsequently stabilise at lower health states, and equally patients classified as stable could continue to decline.
What alternative approach has the ERG suggested?	Assumptions regarding the distribution of health states across which partial responders stabilise is therefore linked to the proportion classified stable, such that that more optimistic assumptions regarding the distribution of stable partial responders likely imply that a greater proportion of patients will be classified as unstable partial responders. Given the optimistic assumptions made by the company regarding the proportion of stabilised partial responders, the ERG considers that scenarios should be explored where patients stabilise across a range of GMFC health states including GMFC 3 and 4.
What is the expected effect on the cost-effectiveness estimates?	In a scenario in which 30% of patients are assumed to stabilised in GMFC 3 and 4: • The ICER increases from [redacted] to [redacted] in the PS-LI population, • The ICER decreases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population,

	• The ICER increase from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	Additional follow up will increase the ability to distinguish between stable and unstable partial responders. Further clinical input on the likely biological plausibility of patients stabilising after experience decline in symptoms may also be informative.

Issue 9 Sub-populations for decision making

Report section	4.2.3.3
Description of issue and why the ERG has identified it as important	Reflecting the marketing authorisation of the OTL-200 the modelled population includes three distinct sub populations: i) pre-symptomatic late infantile; pre-symptomatic early juvenile; and, symptomatic (GMFC <2) early juvenile. In the economic analysis, these three populations are modelled separately to allow for differences in base-line characteristics, natural history and the efficacy of OTL-200 to be reflected. To estimate an ICER for the combined population covered by the marketing authorisation, the ICERs for each group were aggregated as a weighted average based on the expected incidence of patients across the three groups. The ERG considers there to be substantial heterogeneity in cost-effectiveness estimates across the three populations which is not captured when considering a single decision for the whole population. The ERG considers the exploration of these subgroups to be very relevant to decision making and in particular consider it appropriate to consider symptomatic patients separately, given the significant differences in the efficacy of OTL-200 in this population. Results of the elicitation process used to generate the weights applied to each population demonstrate substantial divergence in clinical opinion. Further, the population weights appear inconsistent with epidemiological evidence that suggests that the LI sub-population is the most prevalent. If a single ICER is considered, weights applied to each subgroup ICER should better account for the available epidemiological evidence.
What alternative approach has the ERG suggested?	Decision modelling should consider the distinct sub-populations based on disease phenotype and presence of symptoms at treatment initiation. Where a single ICER is considered the ERG suggests that weights be derived based on an approach that integrates evidence from published epidemiological studies and the elicitation exercise.
What is the expected effect on the cost-effectiveness estimates?	This approach allows for more accurate estimates of cost-effectiveness across sub-populations. Where the distribution of patients is updated in line with available epidemiological, evidence the pooled ICER decreases from [redacted] to [redacted] per QALY gained.

What additional evidence or analyses might help to resolve this key issue?	Further evidence on the incidence of disease and likely uptake of OTL-200 would help inform the proportion of patients eligible for treatment from each subgroup.

Issue 11 Discounting

Report section	4.2.6
Description of issue and why the ERG has identified it as important	The company base-case uses a non-reference discount rate of 1.5% on the grounds that the criteria outlined in the NICE methods guide are met. This is important as the majority of costs associated with OTL-200 are accrued upfront, while benefits are accrued over a long period of time. A substantial proportion of patients in the LI and PS-EJ cohorts will not achieve stabilisation of disease without continued symptom progression, while no patient in ES-EJ group will achieve this. Patients failing to stabilise prior to disease progression will either stabilise with permanent and potential significant disability, or experience continued albeit slowed progression of disease. This cannot be considered as returning patients to full or near to full health. There is significant uncertainty whether stabilisation of disease will be permanent. Durable clinical efficacy has been demonstrated up to 60 months in a small number of patients (n=[redacted]); with a maximum follow-up of 77 months, there are no data beyond this. There is also uncertainty with regards to surrogate markers of treatment efficacy which show some evidence of decline. The substantial upfront costs of OTL-200 mean it commits the NHS to substantial irrecoverable costs in the event of a non-permanent treatment effect. Should patients who currently appear stable begin to experience progression of symptoms, then not only would the full cost of OTL-200 have been incurred, but there will be both significant reductions in the QALY benefits as well as very substantial increases in care costs.
What alternative approach has the ERG suggested?	The standard reference case discount rate of 3.5% should be applied.
What is the expected effect on the cost-effectiveness estimates?	In a scenario where the NICE reference case discount rate of 3.5% is applied to costs and benefits: • The ICER increases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population • The ICER increases from [redacted] to [redacted] in the ES-EJ population • The ICER increase from [redacted] to [redacted] in the pooled analysis

What additional evidence or analyses might help to resolve this key issue?	Further follow up of patients will help establish the durability of stabilisation. Issues relating to the proportion of patients achieving response prior to progression is unresolvable and relates to the effectiveness of OTL-200.

Issue 12 Proportion of full responders and stable partial responders

Report section	4.2.7.1
Description of issue and why the ERG has identified it as important	The company may have overestimated the proportion of full responders and stabilised partial responders. The definition of full response does not require a minimum period of follow up. This means that patients were classified as full responders with only very short follow up. The insensitivity of GMFC categories to slow change means it is difficult to distinguish between stability and slow decline. Several patients classified by the company as stabilised partial responders do not appear to have stabilised. Some patients exhibit a drop in GMFC-MLD level at the most recent follow-up, and others previously declined after a long period of apparent stability. These GMFC trajectories are contrary to the model of action proposed by the company, that is, late stabilising patients undergo an initial period of progression before the treatment effect is established, after which point stabilisation will be permanent. In the ES-EJ sub-population a patient is excluded even though they received treatment and would be otherwise eligible under the marketing authorisation. This exclusion leads to the proportion of stable partial responders being overestimated.
What alternative approach has the ERG suggested?	Establishing a minimum follow-up period is difficult given the limited data. However, given these limitations and evidence on ARSA stabilisation, a period of 12 months would seem reasonable, if optimistic. Patients who have experienced a decline in GMFC score more than 12 months after treatment should be classified as unstable. The excluded patient should be included in all analyses.
What is the expected effect on the cost-effectiveness estimates?	Re-estimating the proportion of responders requiring a minimum of 12 months to establish full response and reclassify any patient as unstable who experienced a decline more than 12 months: • Increase the ICER from [redacted] to [redacted] in the LI population, • Increase the ICER from [redacted] to [redacted] in the PS-EJ population, • Increase the ICER from [redacted] to [redacted] in the ES-EJ population, • Increase the ICER from [redacted] to [redacted] in the pooled analysis.

What additional evidence or analyses might help to resolve this key issue?	As stated in Issue 3 distinguishing between stable and unstable partial responders is difficult due to the lack of long-term data and insensitivity of the GMFC scale to slow decline. Longer follow and a greater understanding of the implications of ARSA activity levels would be helpful to classify patients appropriately.

Issue 13 Estimation of progression modifier in unstable patients

Report section	4.2.7.1
Description of issue and why the ERG has identified it as important	The rate of progression applied in patients designated unstable partial responders informed on of progression rates in the OSR-TIGET natural history cohort and selected OTL-200 patients. This yielded a ratio (progression modifier) to calculate the time patients are modelled to reside in each health state. Despite a request to explain the clarify the derivation of the modifier, the ERG is unclear on which patients from the OTL-200 cohort were used. It appeared that many may have been outside the licensed population. The ERG also has concerns that the TIGET data used to obtain the base transition values may have also introduced bias due to substantial missing data. In this regard, it may have been better to consider the rate of transition between GMFC 2 and 6 due to the lower levels of missing data. For reasons unclear to the ERG, the company also chose to use a different progression in the ES-EJ sub-population which was based on clinical opinion rather than the estimated progression modifier applied in the pre-symptomatic cohorts. This leads to drastically different disease trajectories being assumed between EJ patients diagnosed as pre-symptomatic versus those diagnosed with early symptoms.
What alternative approach has the ERG suggested?	While there may be a case for applying different progression rates, the lack of data makes this difficult, and no justification has been presented in support of the company's approach. The ERG also considers it undesirable to inform clinical effectiveness parameters using clinical opinion. The ERG would therefore recommend that the estimated progression modifier be applied to all cohorts.
What is the expected effect on the cost-effectiveness estimates?	In a scenario where the same set of progression modifiers are applied to pre-symptomatic and early symptomatic EJ patients: • The ICER increases from [redacted] to [redacted] in the ES-EJ population, • The ICER increase from [redacted] to [redacted] in the pooled analysis. In the LI and ES-EJ populations the ICER does not change as the same progression modifier is applied.
What additional evidence or analyses might help to resolve this key issue?	Clarity on which patients informed the estimation of the progression modifier is important and will help validate this approach. Further data on patients who had received OTL-200 would also be informative as the current estimates are based on very small numbers of patients.

Issue 14 Time spent in GMFC 0

Report section	4.2.7.2
Description of issue and why the ERG has identified it as important	The modelled time in GMFC 0 creates inconsistencies between the model and the observed data. For example, the average age patients reach GMFC 1 in the PS-EJ sub-population is 103 months, while those in the OSR-TIGET study are observed to reach GMFC 5 at an average age of 88 months and GMFC 6 at an average age of 109 months. These issues stem from the use of data from other natural history studies and assumptions made to increase consistency between the ES-EJ and PS-EJ sub-populations.
What alternative approach has the ERG suggested?	Time in GMFC 0 should be estimated using data from the OSR-TIGET study and assumed starting age. Because this cannot be done in the ES-EJ sub-population due to the significant differences between the trial population and OSR-TIGET study. The values applied to the PS-EJ cohort should be used in the ES-EJ sub-population.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis where the ERG re-estimated time spent GMFC 0 using starting age (as reported in the CS) and the OSR-TIGET natural history study: • The ICER decreases from [redacted] to [redacted] in the LI population, • The ICER decreases from [redacted] to [redacted] in the PS-EJ population, • The ICER decreases from [redacted] to [redacted] in the ES-EJ population, • The ICER decrease from [redacted] to [redacted] in the pooled analysis. Note that ES-EJ values are applied in the PS-EJ population, as more appropriate values cannot be estimated using the available data.
What additional evidence or analyses might help to resolve this key issue?	Further clarity from the company is required regarding the differences between the ES-EJ patients recruited to the OTL-trial programme and the natural history study. More complete data on the natural history of patients with MLD would also be informative, thought the ERG is unaware of any sources that have not already been identified by the company.

Issue 15 Mortality in functionally stabilised patients

Report section	4.2.7.3
Description of issue and why the ERG has identified it as important	Disease-related mortality was confined to GMFC 6 in the model, such that patients had to pass through all other GMFC states before suffering any disease related mortality. Patients are otherwise modelled to experience mortality rates in line with the general population. This means that patients classed as functionally stable (i.e., full responders and stabilised partial responders) are assumed to have life expectancy in line with the general population. This is important in the context of

	curative assumptions as life expectancy directly impacts on the longevity of the benefits of OTL-200. The ERG considers there to be several reasons to expect that these individuals will experience morality rates in excess of those of the general population. Firstly, the model does not account for the short- or long-term morality risks associated with the myeloablative conditioning regimen that every patient receiving OTL-200 must undergo. Secondly, there is significant uncertainty regarding the assumption that disease progression will be permanently halted. Thirdly, there may be other disease related mortality not directly attributable to progression of the disease, but associated with neuro-disability experienced by stable and unstable partial responders to OTL-200.
What alternative approach has the ERG suggested?	To account for the impact of neuro-disability on mortality, appropriate adjustment should be made to mortality rates. In the appraisal of cerliponase alfa for CLN2, evidence from people who have suffered traumatic brain injuries is used to model a set of SMRs that scaled with the degree of disability. A similar approach should be applied in the current model. The ongoing appraisal of betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia applied a SMR of 1.25 to general population mortality rates to capture the potential impact of myeloablative conditioning.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis where SMRs are applied to account for both the impact of myeloablative conditioning and neuro-disability: • The ICER increases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population, • The ICER decrease from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	In the absence of extensive follow up in a much larger sample it is unlikely that further direct evidence can be identified to resolve this uncertainty.

Issue 16 Use of a non-reference case approach to elicit utility values

Report section	4.2.8.2
Description of issue and why the ERG has identified it as important	In the absence of existing data on the health-related quality of life (HRQoL) of patients with MLD, the company commissioned an elicitation study to generate health state utilities. The study relied on vignettes to elicit utilities from members of the general public. The ERG considers that the approach adopted by the company to be inconsistent with the NICE reference case and that the utility values generated are unfit for decision making. The company appear to have misunderstood the reference case brief, and the resulting value set

	captures only public preferences and includes no explicit consideration of the quality of life of patients themselves. The ERG notes a number of issues with the vignettes used to elicit utilities in the time trade off (TTO) exercise described by the company, with evidence of unusual responses that tend towards the best and worst possible ratings. These issues manifested in results which appeared to correspond poorly to external data sources.
What alternative approach has the ERG suggested?	The ERG recommends that the company reconsider the methods used to elicit utilities, and to undertake an exercise in line with NICE methods guidance, and with other appraisals of similar conditions (e.g. HST12).
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER is unknown as the direction and magnitude of the bias resulting from the bias is not clear. The direction of this bias may also not be consistent across health states.
What additional evidence or analyses might help to resolve this key issue?	The applied utility set is not fit for purpose and requires significant revision. As outlined above the ERG recommends that a further elicitation exercise be completed.

Issue 17 Application of separate LI utility set

Report section	4.2.8.3
Description of issue and why the ERG has identified it as important	To reflect the fact cognitive decline is less predictable in patients with EJ MLD separate cognitive impairment sub-states were modelled for PS-EJ and ES-EJ patients. These were not applied in the LI population as cognitive decline accompanies deterioration of gross motor function more predictably. This approach leads to patients in the LI cohort being assigned a different utility set until patients reached the age of 48 months. Descriptions of equivalent GMFC stages in the vignettes used to elicit utilities for LI and EJ MLD lacked important context and varied significantly, leading to inconsistencies in the utilities generated. This meant modelled HRQoL jumped significantly when they moved from the LI to the EJ utility set. The ERG requested that these discrepancies be resolved at the clarification stage. The company's revised model instead applied LI utilities for the entire duration of the model. The ERG considers this clearly inappropriate, and only serves to exacerbate the issue of applying different utility values to patients in the same health state. The ERG further considers that the use of a separate LI utility set a needless addition that only serves to increase model complexity and decision uncertainty.
What alternative approach has the ERG suggested?	The ERG considers that the separate LI utility set should be removed from the model as the EJ utility set is sufficient to represent the HRQoL of patients with MLD.
What is the expected effect on the cost-effectiveness estimates?	In a scenario analysis where the LI utility set is replaced with EJ utility: • The ICER decreases from [redacted] to [redacted] in the LI population,

	• The ICER decreases from [redacted] to [redacted] in the pooled analysis. The ICER does not change in EJ sub-populations as these already apply the EJ utility set.
What additional evidence or analyses might help to resolve this key issue?	No additional analysis evidence is required.

Issue 18 Face validity of utility values and cognitive impairment decrements

Report section	4.2.8.4
Description of issue and why the ERG has identified it as important	The applied utility values make extensive use of negative utility values and imply extreme suffering in patients with late-stage disease and limited cognitive function. This is driven in part by a large and independent effect of cognitive impairment upon the modelled utilities. The ERG is concerned that these estimates reflect public perceptions of cognitive impairment, and not how a patient with cognitive impairment feels themselves. This is evidenced by the fact that a substantial proportion of participants would rather die immediately than ever experience cognitive impairment even if otherwise healthy. The decrements applied are also inconsistent with evidence from other diseases where severe cognitive impairment (resulting in almost continuous unconsciousness) and complete loss of motor function are considered for modelling purposes as having a 'near-death' quality of life. More generally the ERG takes issue with use of such strongly negative utilities, which fall well below the lowest utility ascribed to the worst EQ-5D health state as valued by the UK general public. While the ERG appreciates the particular difficulties associated with living with MLD, comparison with health states in other disease areas suggests a lack of external validity.
What alternative approach has the ERG suggested?	The ERG considers that the cognitive impairment decrements should be removed or restricted to health states where patients have a degree of motor function.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis where: HRQoL is determined only by GMFC score i.e. no independent effect of cognitive impairment: • The ICER decreases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population, • The ICER increase from [redacted] to [redacted] in the pooled analysis. Note in the LI population this scenario applies the EJ utility set to LI patients. This is why the ICER is decreased in this population.

What additional evidence or analyses might help to resolve this key issue?	Further clinical input on the HRQoL of patients may help validate the applied decrements. As suggested in Issue 16 the ERG recommends that the value set is revised and based on an elicitation exercise in line with NICE methods guidance.

Issue 19 Age adjustment of utility values

Report section	4.2.8.5
Description of issue and why the ERG has identified it as important	There are two errors in the company's interpretation and application of age adjustments in the model. Firstly, utilities were only adjusted as patients aged in GMFC 0, and only for those with normal cognitive function. This means that utility values applied in GMFC 1-6 are not independently adjusted for age, and remain constant throughout the model. Secondly, the Ara and Brazier predictive equation has been inappropriately used to extrapolate the relationship between HRQoL and increasing age outside of the sample upon which it was based. The approach taken by the company assumes that HRQoL peaks at birth (using a utility derived from adults), and deteriorates from patients' first birthday.
What alternative approach has the ERG suggested?	Age adjustment of utility values should apply to all health states and should be confined to adults to reflect the fact that age related decrements represent the increasing burden of co-morbidities people experience as they age.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis where the two above issues are corrected: • The ICER increases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population, • The ICER increase from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	No further evidence required.

Issue 20 Carer utility decrements

Report section	4.2.8.6
Description of issue and why the ERG has identified it as important	The company model applies utility decrement to account reduction in carer quality of life. Currently, these decrements are, however, only applied once a patient reaches GMFC Stage 5.

	The ERG is satisfied that care of children with MLD is likely to represent a significant burden on families but considers that company appear to have misinterpreted clinical opinion over the necessity and extent of parental care throughout the earlier stages of MLD. Clinical advice received by the ERG indicated the physical burden of feeding, supervising, and managing children in the earlier stages of the condition mean that it would be more appropriate to apply a caregiver disutility from GMFC 1 onwards.
What alternative approach has the ERG suggested?	Application of carer utility decrements in less severe health states.
What is the expected effect on the cost-effectiveness estimates?	In scenario where the number full-time carers is modified such that a full time care and supervision from at least one parent would be necessary from GMFC 2 onwards, with at least some impact upon the health and mental wellbeing of caregivers of patients in GMFC 1: • The ICER increases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population, • The ICER increase from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input on the physical and mental burden of carer responsibilities may clarify when any decrements should be applied.

Issue 21 Resource use applied in GMFC 0

Report section	4.2.9.2
Description of issue and why the ERG has identified it as important	The cost-effectiveness analysis in the company's original submission did not include any MLD-related resource use costs for patients in GMFC-MLD 0. While these patients may be restored to near general population health, the ERG does not consider it reasonable to assume that there would be no monitoring of patients previously diagnosed with a life-threatening condition and treated with myeloablative conditioning and gene therapy. For example, the SmPC states that the patient should be monitored for any signs of leukaemia or lymphoma during the routine yearly check-ups. As discussed in relation to Issue 6, GMFC scores may be overly simplistic and fail to capture other manifestations of the disease which are treated sub-optimally by OTL-200. Patients classified as functionally stabilised may therefore continue to experience manifestations of disease such as hepatobiliary disorders, metabolic acidosis, and renal tubular acidosis resulting in additional costs to the NHS.

What alternative approach has the ERG suggested?	Health state costs should be revised to account for both the additional monitoring patients are likely to undergo. The impact of myeloablative conditioning and non-GMFC manifestations should also be included.
What is the expected effect on the cost-effectiveness estimates?	The addition of costs to the health state will increase the ICER. It is difficult to establish the long-term care needs of these patients given the limited data and clinical experience of using gene therapies.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on markers of disease in functionally stabilised patients would help inform the health care needs of these patients.

Issue 22 Resource use applied patients with late stage disease

Report section	**4.2.9.2**
Description of issue and why the ERG has identified it as important	In GMFC-MLD 6, the company's analysis assumes that 80% of patients are cared for in their home, with the remaining 20% of patients are cared for in hospital or a hospice full time. The company further assumes that hospitalised patients will receive substantial additional social care provision amounting to 7.2 hours per day 292 days per year. This results in care costs of patients being estimated to be over £800 per day in hospitalised patients and significantly increases care costs applied in the GMFC 6 health state. Clinical advice received by the ERG suggested that residential hospital care for patients with MLD is extremely rare and that typically patients with end stage disease will be cared for in the home. Patients will only require hospitalisation for resolving specific medical needs, such as to manage a status epilepticus, gastrostomy fitting, or to treat a serious infection. In this regard, the ERG notes that model already accounts for hospitalisation costs for patients cared in the home and that these costs are likely to better reflect these incidences of hospitalisation. The ERG therefore does not consider it appropriate to model any patients as being in residential hospice or hospital accommodation. Further the ERG does not agree that it is appropriate to add additional social care costs for patients who are cared for in a hospital or hospice setting and considers that any care needs will be covered by hospital/hospice costs already applied. The ERG therefore considers that these costs should be removed if residential hospital care is permitted.
What alternative approach has the ERG suggested?	Assumptions on the proportion of patients in GMFC receiving residential hospital care should be revised to zero, assuming instead that all patients are cared for in the home.
What is the expected effect on the cost-effectiveness estimates?	In the ERG preferred scenario where all patients in GMFC 6 are assumed to be cared for in a home setting: • The ICER increases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population,

	• The ICER increase from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	Further input from clinical experts may help to inform the care requirements of patients with end stage disease.

Issue 23 Resource use for adults with symptomatic MLD

Report section	4.2.9.2
Description of issue and why the ERG has identified it as important	The model predicts that there are a significant proportion of patients who receive OTL-200 will achieve a partial response and consequently either experience long-term disability or continued slow decline. Due to the benefits of OTL-200 many of the patients are likely to survive into adulthood. The company analysis, however, assumes that resource use in adult patients is largely the same as those for children in the equivalent health state. This may not be reasonable. Consultation with the ERG clinical advisor suggest that it is likely that an adult in health states GMFC-MLD 2 or worse will require some degree of care from social services. And that from GMFC3 onwards, it would not be possible for patients to live independently and would require either significant in-home assistance or institutional care.
What alternative approach has the ERG suggested?	The model should acknowledge that the care needs of adults may be different to children and that patients may be less reliant on family support and more reliant on social services, and in more severe health states may require residential care.
What is the expected effect on the cost-effectiveness estimates?	In the ERG scenario in which a proportion of adult patients is assumed to be cared for in an institutional setting: • The ICER increases from [redacted] to [redacted] in the LI population, • The ICER increases from [redacted] to [redacted] in the PS-EJ population, • The ICER increases from [redacted] to [redacted] in the ES-EJ population, • The ICER increase from [redacted] to [redacted] in the pooled analysis.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on resource use in adults with MLD may be helpful. This could potentially be informed by care needs with less aggressive adult onset forms of the disease.

1.6 Other key issues: summary of the ERG's view

Issue 10 Potential impact of OTL-200 on diagnosis and screening

Report section	4.2.3.4

Description of issue and why the ERG has identified it as important	Clinical advice to the ERG suggested that the availability of an effective treatment for MLD would encourage earlier diagnosis of the condition. Currently some cases are not diagnosed until symptoms develop because there is no effective treatment. Having treatment may encourage parents and physicians to pursue earlier diagnosis, before symptom onset, which could maximise the effectiveness of OTL-200 treatment. The availability of treatment might also encourage the use and development earlier testing and screening for MLD, which would further ensure prompt pre-symptomatic treatment.
What alternative approach has the ERG suggested?	Not relevant
What is the expected effect on the cost-effectiveness estimates?	There is currently, no evidence to inform the effect of new born screening on the effectiveness of OTL-200. The ERG, however, agrees broadly with the company that the introduction of new-born screening would positively impact on the effectiveness of OTL-200 and would improve cost-effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Not relevant

1.7 Summary of ERG's preferred assumptions and resulting ICER

The ERG's alternative base-case analysis combines a number of the above scenario analyses. This includes Scenarios 1, 2 (affects pooled ICER only), 3, 5a, 6, 7, 8, 9, 10a, 11, 12, 13, 14b, 15. The results of the ERG base case are presented in Table 1.

Modelling errors identified and corrected by the ERG are described in Section 5.3 For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.

Table 1 Deterministic Results of ERG scenario analyses

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
ERG corrected base case																
BSC	[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]
ERG Scenario 1: Cognitive decline linked to GMFC progression in OTL-200 patients																
BSC	[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]
ERG Scenario 2: Alternative MLD subtype distribution																
BSC	[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]
ERG Scenario 3: Discount rate of 3.5% for costs and benefits																
BSC	[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]
ERG Scenario 4a: Stability persists for 100 years on average																
BSC	[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]
ERG Scenario 4b: Stability persists for 50 years on average																
BSC	[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]
ERG Scenario 4c: Stability persists for 20 years on average																
BSC	[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]
ERG Scenario 4d: Stability persists for 10 years on average																

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
BSC	[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]
ERG Scenario 5a: Patients with <12 months follow-up excluded																
BSC	[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]
ERG Scenario 5b: Patients with <12 months follow up and decline classed as unstable partial responders																
BSC	[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]
ERG Scenario 6: Equivalent progression modifiers applied in ES EJ and PS EJ patient																
BSC	[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]
ERG Scenario 7: Re-analysis of OSR-TIGET health state residence times																
BSC	[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]
ERG Scenario 8: Incorporation of neuro-disability-related and myeloablative conditioning SMRs for patients in GMFC 1-5																
BSC	[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]
ERG Scenario 9: Updated survival models based on pooled LI/EJ data in GMFC 6																
BSC	[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]
ERG Scenario 10a: HRQoL determined only by GMFC score (no independent effect of cognitive impairment)																
BSC	[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	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
ERG Scenario 10b: Cognitive impairment decrements applied only in GMFC 0 – 2																
BSC	[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]
ERG Scenario 11: EJ utilities applied to LI patients																
BSC	[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]
ERG Scenario 12: Age adjustments removed from patients aged <16 and applied to all patients regardless of GMFC stage																
BSC	[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]
ERG Scenario 13: Caregiver decrements applied at an earlier stage of disease																
BSC	[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]
ERG Scenario 14a: Additional costs of social care removed from hospitalised patients																
BSC	[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]
ERG Scenario 14b: Assume all patients in GMFC 6 are cared for primarily in a home setting.																
BSC	[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]
ERG Scenario 15: Adult social care costs include institutional care																
BSC	[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]
BSC	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Base-case Scenario 1:1.5% discount for costs and benefits																
BSC	[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]
ERG Base-case ERG Scenario 2a: Stability persists for 100 years on average																
BSC	[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]
ERG Base-case ERG Scenario 2b: Stability persists for 50 years on average																
BSC	[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]
ERG Base-case ERG Scenario 2c: Stability persists for 20 years on average																
BSC	[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]
ERG Base-case ERG Scenario 2d: Stability persists for 10 years on average																
BSC	[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]
ERG Base-case Scenario 3: Apply LI utility set to EJ patients																
BSC	[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]

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report the ERG has reviewed the clinical and cost-effectiveness evidence submitted by Orchard Therapeutics in support of OTL-200 for the treatment of metachromatic leukodystrophy (MLD) in asymptomatic children with late-infantile or early-juvenile disease onset, or in children with early symptoms with early-juvenile onset. In this section the ERG critiques the company's proposed positioning of OTL-200 in the treatment pathway and its definition of the decision problem when compared with the NICE scope.

2.2 Background

The CS stated that in England, MLD patients are managed by local paediatric specialists who refer patients to one of the three paediatric lysosomal storage disease specialist centres for expert treatment. The company also stated that it is in discussions with NHS England regarding the qualification of one of these three centres for administration of OTL-200. Changes to the existing clinical care pathway were expected to be minimal and not to involve significant alteration to current service provision. Some patients are diagnosed pre-symptomatically following screening as a result of an older sibling being diagnosed with MLD.

The CS stated that available treatments options are currently limited to supportive/palliative care, adding that the use of allogeneic HSCT has been limited to patients with late-onset variants (i.e. late-juvenile and adult patients), given the slower rate of disease progression in the early stages and the lack of treatment alternatives. However, prior to OTL-200 becoming a licensed treatment there was also a lack of treatment alternatives for LI and EJ patients and some EJ patients may also have slow rates of disease progression. The ERG's clinical adviser considered that there are centres that would offer HSCT to genuinely pre-symptomatic infants and children, with counselling given to the family advising that it would not be a cure. The ERG's clinical adviser added that if there were a choice between allogeneic HSCT and gene therapy, gene therapy would be preferred. OTL-200 should therefore be viewed as a replacement for allogeneic HSCT in the treatment pathway. Its likely advantages over HSCT appear considerable, having the potential to be curative for some patients and in being applicable to a broader subgroup of MLD patients than HSCT currently is.

2.3 Critique of company's definition of decision problem

2.3.1 Population

In terms of age groups, OTL-200 is licensed for 'late infantile' and 'early juvenile' MLD patients, though not for 'late juvenile' patients. In the CS, specific reference was made to the Kehrer et al., 2020 paper[1] when describing the classification of juvenile forms of MLD. This paper defined the upper age limit of symptom onset for classifying patients as 'early juvenile' (EJ) as being <6 years old. The ERG noted that the company trial cohorts differ slightly from this, using <7 years old as an upper cut-off for early juvenile classification.

The ERG asked the company to clarify the use of <7 years instead of <6 years. The company cited five papers to support the <7 years definition: one (Sessa 2016) was an early paper on the OTL-200 trial cohort (when the therapy was licensed to GSK). Three of the remaining papers seemed to indicate an age cut-off of <6 years old, although this was not totally clear with the wording being *before or after 6 years of age* or similar (Biffi et al 2008, Rosenberg et al 2016, Sevin et al 2007). In the last paper the cut-off was somewhat blurred *early-juvenile (2–6 years), late-juvenile (6–16 years)* (Solders et al. 2014). The ERG's clinical adviser stated that the age category terms are used relatively loosely and that the one-year difference between the definitions was not likely to be important in clinical practice. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) assessment report[2] also notes that "*the arbitrary classification of MLD is particularly applicable to the stratification of juvenile forms into early and late juvenile*". Given this uncertainty over the classification of juvenile forms of MLD, the ERG infers that the EMA license relates to patients <7 years of age - to reflect the OTL-200 trial eligibility criteria - though notes that only one patient who received OTL-200 had an age of onset between their 6th and 7th birthdays.

The definition of what constitutes an early symptomatic patient was somewhat unclear. The EPAR stated that "*early symptomatic was initially defined as within 6 months after the first reported symptom, and later as subjects with an intelligence quotient ≥70 and the ability to walk independently for ≥10 steps. In the discussion of efficacy results, early symptomatic is referred to as patients meeting the eligibility criteria for treatment, i.e. IQ ≥ 85 and GMFC-MLD ≤1. i.e. treatment should only be initiated if the patient has the ability to walk independently and before the onset of cognitive decline*".

2.3.2 Intervention

OTL-200 is an autologous CD34+ haematopoietic stem and progenitor cell gene therapy. It is administered once, intravenously following a myeloablative conditioning regimen (use of busulfan is recommended). The minimum recommended dose of OTL-200 is 3×10^6 $CD34^+$ cells/kg. The product formulation has changed from being a fresh product to a cryopreserved product, which is the intended

commercial formulation. Most of the submission data relate to the fresh product. The cryopreserved product was assessed in a separate clinical study of [redacted] patients, with limited follow up.

Being an autologous therapy OTL-200 is manufactured for patients individually. Figure A3 in the CS summarises the process which consists of: blood cell collection, shipment to manufacturing facility, cell isolation, lentivirus transduction, cryopreservation, return shipment, busulfan conditioning chemotherapy and patient infusion. Patients remain at the treatment centre between 4 and 12 weeks from beginning of conditioning to discharge. The EPAR noted that the conditioning regimen initially implemented consisted of 14 doses of busulfan (according to subject's weight; submyeloblative conditioning regimen (SMAC)) and that this was modified to reduce the variability of transduced cell engraftment and designed to produce a higher cumulative busulfan AUC. This new conditioning regimen consisted of body surface area-based dosing of busulfan according to the subject's age (myeloablative conditioning regimen (MAC)).[2]

2.3.3 Comparator

The CS excluded HSCT as a comparator on the basis of "evidence from clinical experts, patient groups and the literature indicate that stem cell transplant is not used in LI or EJ MLD patients." The expert opinion was based on a study of 6 clinicians which was funded by the manufacturer. This reported that an estimated 4% of LI patients and 16% of EJ patients would be treated with HSCT in clinical practice. The ERG thinks these figures may underestimate the prevalence of HSCT due to the wording of the questioning. The experts were asked: "*What proportion (%) of EJ patients would be treated with HSCT in clinical practice?*". The same question was asked about LI patients. A more appropriate question would have been: "*What proportion (%) of EJ patients eligible for treatment with OTL-200 would be treated with HSCT in clinical practice?*" or "*What proportion of EJ patients who are pre-symptomatic, or have early clinical manifestations, would be treated with HSCT in clinical practice?*".

The case for not using HSCT is made most strongly for symptomatic EJ patients or pre-symptomatic LI patients on the basis that replacement of ARSA deficient host cells by ARSA producing donor cells is too slow relative to the pace of disease progression (p76, CS). However, data from the long-term study by Groeschel et al 2016[3] suggest that patients who underwent HSCT at GMFC-MLD levels 0 and 1, patients with an IQ of at least 85, and patients with an age at onset older than 4 years had a better chance of developing stable disease following HSCT. These characteristics are very similar to EJ population eligibility criteria described in the EMA license. Moreover, a mini-review by Helman et al, based on a Global Leukodystrophy Initiative (GLIA) consensus meeting, reported that although the use of HSCT has been widely debated due to phenotypic variability, transplant-refractory

peripheral neuropathy, high treatment-related morbidity and mortality, and limited long-term outcome data, the most substantial disagreement centres on HSCT use in LI MLD patients.[4]

Given that the ERG's clinical adviser also considered that HSCT may sometimes be a treatment option in genuinely pre-symptomatic patients, the ERG disagrees with the company's decision to completely remove HSCT as a comparator treatment from the submission, especially for PS-EJ patients. This issue is also discussed in Section 3.2.6.2 (comparator cohort).

2.3.4 Outcomes

Although some results data were reported for each of the outcomes listed in the NICE scope, the ERG's access to data and to important methodological details relating to outcomes was limited. In light of this the ERG cannot rule out the possibility that selective reporting of data and results may have adversely affected the appraisal. The ERG notes in particular a lack of useful baseline data for all patients (essential for evaluating comparative outcomes), a lack of detail in how data were derived for the natural history group dataset, and a lack of individual patient data which would have provided useful insights about how outcomes change over time in individuals treated with OTL-200.

Table 2 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with MLD	People with the following forms of MLD • Late Infantile (LI) or Early Juvenile (EJ) forms, without clinical manifestations of the disease, hereby referred to as pre-symptomatic Late Infantile (PS LI) and pre-symptomatic Early Juvenile (PS-EJ) patients • EJ form with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline, hereby referred to as early-symptomatic early juvenile (ES-EJ) patients	The proposed population is in line with the anticipated licensed indication shown below, for which the CHMP has granted a positive opinion OTL-200 is indicated for the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of ARSA enzymatic activity: • in children with LI or EJ forms, without clinical manifestations of the disease, • in children with the EJ form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline The population in the scope includes patients with Late Juvenile (LJ) and adult MLD variants who would not be eligible for treatment with OTL-200.	The ERG agrees with the company's rationale.
Intervention	OTL-200	OTL-200	N/A	There has been a change in formulation from a fresh product to a cryopreserved product. Most of the efficacy and safety data relate to the fresh product. See Section 3.2.5
Comparator(s)	Established clinical management without OTL-200, including but not limited to: • Stem cell transplant	Established clinical management without OTL-200 which includes best supportive care. Stem cell transplant is not considered an appropriate comparator.	Evidence from clinical experts, patient groups and the literature indicate that stem cell transplant is not used in LI or EJ MLD patients. It is only used in LJ and Adult patients who would not be eligible for treatment as per the licensed indication. As	The ERG disagrees with the total exclusion of allogeneic HSCT as a comparator.

	• Best supportive care		such, stem cell transplant is not included in our submission as a comparator. More details for why the stem cell transplantation is not a suitable comparator for OTL-200 are provided in Section 8.2. of the CS.	
Outcomes	• change in gross motor function • change in neurological function • change in neurocognitive function • change in ARSA activity • stability of nerve conduction • age and time at severe motor impairment or death • mortality • adverse effects • health-related quality of life (for patients and carers)	Same as scope but see ERG comment	N/A	The CS reports data relating to each of the outcomes listed in the scope. However, the data reported were often limited. Given the small number of patients studied, the ERG requested much more detailed data to clarify this uncertainty. However, the data requests were only partly fulfilled by the company, resulting in remaining uncertainty about certain clinical efficacy outcomes.
Economic analysis				
Subgroups	• Pre-symptomatic MLD • Early-symptomatic MLD	• Pre-symptomatic Late Infantile MLD (PS LI) • Pre-symptomatic Early Juvenile MLD (PS-EJ) • Early symptomatic Early Juvenile MLD (ES-EJ)		The ERG's clinical adviser considered that 'Late Infantile' and 'Early Juvenile' were now accepted definitions for use in clinical trials though in practice they form part of a spectrum. The ERG did not consider the upper age limit of 7 for early juvenile to be an issue.
Special considerations including issues				

related to equity or equality				

3 CLINICAL EFFECTIVENESS

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review. The ERG notes that the systematic review commissioned by the company[5] cited the CSR for the main registrational study of OTL-200 (201222, reference 34 in the systematic review) a CSR for the expanded access programmes (reference 11 in the systematic review) and an abbreviated CSR for the study of the cryopreserved formulation of OTL-200 (reference 42 in the SR). Although CSRs were requested by the ERG they were not provided by the company.

3.1 Critique of the methods of review

3.1.1 Searches

The search strategies reported in Appendix B of the CS covered the identification of published and unpublished studies relating to MLD. This broad approach would have identified studies relating to the effectiveness, safety and adverse effects of any treatments for MLD as well as studies of health-related quality of life and health economics relating to MLD. The ERG appraisal is presented in Table 3.

Table 3 ERG appraisal of evidence identification

Topic	ERG response	Notes
Is the report of the search clear and comprehensive?	Yes	Very clear and mostly comprehensive reporting of the searches. Missing: - Cochrane Central Register of Controlled Trials (CENTRAL) strategy - missing from Appendix B of the submission. Found in the original systematic review of treatments for MLD by Kleijnen Systematic Reviews.[5] - Northern Light Life Sciences Conference Abstracts strategy - missing from Appendix B of the submission and not included in the original systematic review by Kleijnen Systematic Reviews. [5]
Were appropriate sources searched?	Yes	Sources searched provided coverage of the health/medical/economics literature and included sources of both published and unpublished studies: - 9 databases (including 2 databases of conference abstracts) - 2 trial registers. The WHO International Clinical Trials Registry Platform (ICTRP) was unavailable to search due to the current pandemic. - Reference checking of included studies and other systematic reviews were checked to identify further studies
Was the timespan of the searches appropriate?	Yes	- Database searches covered the period from database inception to May 2020 - Conference abstract searches - 2018-2020 - Trials register searches – register inception to May or June 2020

Were appropriate parts of the PICOS included in the search strategies?	Yes	MLD (P)
Were appropriate search terms used?	Yes	Textword searches and subject headings for MLD were included. Various synonyms and alternative terms for MLD were incorporated.
Were any search restrictions applied appropriate?	NA	Searches were not restricted by date, language or study design.
Were any search filters used validated and referenced?	NA	Searches did not include any search filters.

NA Not applicable

3.1.2 Inclusion criteria

The inclusion criteria were appropriate and reflected the NICE scope, including HSCT as a comparator. The criteria for best supportive care covered any of the following: management of dystonia, infections, seizures or secretions; pain relief/sedative drugs; feeding support (including gastrostomy); psychological and social support (including specialist schooling); coordination of the multidisciplinary team and community care; genetic advice and planning; and end of life care.[5]

3.1.3 Critique of data extraction

Data extraction methods were appropriate, being performed by two reviewers working independently. Any discrepancies were resolved through discussion or the intervention of a third reviewer.

3.1.4 Quality assessment

The methods of quality assessment were also appropriate, utilising the Joanne Briggs Institute (JBI) Critical Appraisal Checklist for Non-randomised Experimental Studies. Two reviewers independently carried out each assessment and any discrepancies were resolved through discussion or the intervention of a third reviewer.

3.1.5 Evidence Synthesis

A narrative synthesis was conducted, which was appropriate given the nature of the data. Data from the OTL-200 studies and programmes were pooled and discussed as an integrated population which is equivalent to conducting an unweighted meta-analysis. The CS stated that this approach was deemed acceptable by the EMA considering that comparable protocols, the same drug product formulation, schedule of assessments, and endpoints were used, and the same clinical team were responsible for the enrolment, treatment and follow-up of subjects.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1 Studies on the clinical efficacy and safety of OTL-200

Figure C1 in the CS, reproduced here as Figure 1, summarises the trial/programme names and the numbers of patients each contributed to the integrated data set (IDS) and the safety data set. The IDS was comprised mostly of patients from the main registrational study (study 201222, NCT01560182, which used the fresh formulation of OTL-200) and was supplemented by data from two compassionate use programmes and one hospital exemption programme. Data relating to the commercially available cryopreserved formulation were derived from six patients. The studies and programmes had single-arm designs; an age and disease variant-matched natural history population was used as a comparator group (see Section 3.2.6.1).

Figure 1 Flow of patients contributing to the OTL-200 efficacy and safety datasets (reproduced from the CS)

Twenty-two patients were screened and enrolled into the largest study: 201222. Two patients withdrew prior to receiving treatment: one was due to withdrawal of parent consent and the other due to rapid disease progression. Co-primary endpoints were improvement ≥10% in total gross motor function measure (GMFM) score compared to historical control, and significant (≥2 SD) increase in residual ARSA Activity compared to pre-treatment values, measured in peripheral blood mononuclear cells (PBMCs) at 2 years after treatment. Secondary outcomes were numerous and included: GMFC-MLD levels, Nerve conduction velocity 2 years after treatment, total brain magnetic resonance imaging (MRI) score 2 years after treatment and IQ > 55 at 24, 30 and 36 months.

The ERG asked for more details about why [redacted] patients were excluded from the indicated population (i.e. excluded from the efficacy analyses). The company stated that the efficacy analyses included only patients who would meet the eligibility requirements for treatment with OTL-200, as specified in the SmPC, and that these four patients did not meet these requirements. The ERG agrees that [redacted] patients would not be eligible for an infusion due to their baseline assessment data: [redacted].

The ERG considers that the fourth patient [redacted] would still be eligible to receive treatment in clinical practice and should be included in the Indicated Population Dataset analyses. The company stated that [redacted]. The company stated that this exclusion was based on Section 4.4. and Section 5.1. of the SmPC. Section 4.4 of the SmPC is headed "Special warnings and precautions for use"; the company excludes patient MLD 21 because "*physicians should ensure no deterioration has occurred between screening and commencement of cellular harvest*." However, early symptomatic patients are likely to deteriorate to some extent and since the company's quote comes from the section sub-headed *Rapidly progressive phase of the disease* the ERG interprets this reason for exclusion as relating specifically to patients deemed to have entered a rapidly progressing phase before a Libmedly infusion. The company supplied no data to justify the claim of "rapid progression" before cellular harvest and treatment for this patient. The clearest evidence that [redacted] should be included in the Indicated Population Dataset comes from p182-3 of the company's "Summary of clinical efficacy" report,[6] which described how the change in GMFC-MLD data over time indicated that [redacted] (emphasis added), and [redacted]. The SmPC[7] also states (when discussing treatment failures) that of the three early-symptomatic EJ patients who showed deterioration in both motor and cognitive functions comparable to that observed in untreated patients "two out of the three patients showed deterioration between screening and baseline (onset of conditioning regimen) assessments". The implication being that one deteriorated after treatment.

3.2.2 Patient Characteristics

The CS had critical gaps in the clinical data reported, both in terms of baseline data and trial results. Given the small number of patients studied, the ERG requested individual patient data (IPD), if available, or a clearer summary presentation of data if IPD were not available. The company stated that IPD were only available for the six patients in the study of the cryopreserved formulation but did not present baseline data for any of the study cohorts apart from very limited data in a 1065-page appendix and a 228-page 'Summary of clinical effectiveness' report submitted by the company in response to the ERG's points for clarification questions. The EMA's EPAR was published online after the company's submission.[2] This did contain baseline IPD, split by subgroup, for the 20 patients in the '20122' registrational study. Key details are presented in Table 4 and Table 5. The ERG's clinical adviser was asked to comment on the population baseline characteristics in terms of their applicability to patients seen in the NHS; he considered the characteristics of the studied population was broadly applicable to the NHS. He also thought that, should OTL-200 be approved in the NHS, and

consequently earlier testing introduced, the age at diagnosis might decrease for some pre-symptomatic patients who have affected older siblings (since currently some parents choose not to have a newborn tested, given the limited treatment options). This should result in earlier treatment times than were seen in the OTL-200 studies, which might improve outcomes.

Table 4 Baseline data for Late Infantile MLD patients in trial 20122

	Subject number								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Gender	male	male	male	female	female	male	female	female	male
Age (months)	15	13	7	17	12	16	23	9	8
Age of onset	18	24-27	15	19	15-18	20	26	24-27	24-30
Months from treatment to onset	3	approx 12	8	2	approx 4	4	3	approx 18	approx 18
Sibling survival (months)	61.3	68.4	42.4	51.8	74.7	-	75.8	68.4	-
Sibling status	died	died	died	withdrew	died	NE	alive	died	NE
ARSA in PBMCs	3.27	10.92	3.17	5.13	16.67	NA	9.85	4.23	2.98
GMFM score (%)	65.0	75.6	27.3	80.1	75.0	66.0	71.1	51.0	20.9
GMFC-MLD level	NA	NA	NA	NA	NA	NA	1	NA	NA
NCV Index	-9.79	-0.47	-3.38	-0.16	-6.06	-6.02	-3.11	-1.28	-4.86
Total MRI score	0	0	0	0	0	0	2.25	0	0.25
IQ (Performance)	95	115	100	105	95	100	80	95	95
IQ (Language)	NA	83	112	109	109	94	89	127	106

NA Not applicable, NE Not enrolled

Table 5 Baseline data for Early Juvenile MLD patients in trial 20122

	Subject number										
	10	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Status (variant)	Pre-symptomatic (PS-EJ)					Early-symptomatic (ES-EJ)					
Gender	female	female	male	male	female	male	female	male	female	female	female
Age (months)	18	66	48	66	59	38	88	139	84	69	71
Age of onset	24-36	83	61	75	54	35	66	64	56	60	65
Months from onset to treatment	approx -24	-17	-13	-9	5	3	22	75	28	9	6
Sibling survival (months)	211	147.8	97	104.3	NA	NA	NA	127.4	NA	NA	NA
Sibling status	alive	alive	alive	alive	NA	NA	NA	alive	NA	NA	NA
ARSA in PBMCs	17.86	5.41	4.07	0.69	5.33	18.39	3.45	14.45	27.98	12.04	8.56
GMFM score (%)	77.9	97.3	95.7	98.6	73.9	87.1	99.4	86.1	86.8	81.2	78.0
GMFC-MLD level	0	0	0	0	1	1	0	1	1	1	1
NCV Index	-10.25	-3.89	-3.1	-3.14	-7.58	-4.73	-9.51	-9.27	-8.86	-7.93	-3.17
Total MRI score	0	3.5	4.25	3.75	11	0.5	8.75	4	12	10	10
IQ (Performance)	90	127	124	115	50	100	119	115	89	82	87
IQ (Language)	79	107	130	118	76	103	110	102	104	102	112

NA Not applicable

For the late infantile subgroup baseline ages ranged from 7 to 17 months. Six of the eight patients had sub-myeloablative conditioning and two had myeloablative conditioning. Total MRI scores were zero in all but one of the patients (a score of zero indicates no demyelination of the CNS), but NCV index scores were below the normal range (which is between 1 and -1) in all except two patients, indicating peripheral neuropathy. Moreover, four of the eight LI patients were noted to have abnormal neurological exam findings at baseline.[2]

The early juvenile patients had similar NCV Index scores to the PS-LI subgroup, with no patients having scores within the normal range. However, total MRI scores were very different to the PS-LI subgroup with only one patient having a score of zero. Significant patient heterogeneity was evident in the early-symptomatic early-juvenile subgroup with the time between symptom onset and OTL-200 treatment ranging from 3 to 75 months.

3.2.3 Quality assessment of the OTL-200 studies

All the included studies were small, open-label, single-armed studies so were inherently at high risk of bias and subject to lack precision in their results. Nevertheless, given the rarity of MLD, the study designs used were unavoidable. Critical appraisals of the OTL-200 studies were presented in Section 9.5 of the CS.

The ERG disagrees with some of the company's appraisal decisions. Table C5 of the CS states that "results are presented for each patient" for study 201222. This is not the case, certainly not for all outcomes and timepoints, despite the ERG requesting such data at the clarification stage of the appraisal. In light of this, the ERG has concerns about bias arising from selective outcome/result reporting.

The ERG also thought that consideration of the impact of confounding between the population receiving OTL-200 and the age and disease variant-matched natural history population (the main comparator group) was not well presented in the CS. Ideally, a list of important key confounders would be identified followed by attempts to match patients based on such a list. The main control group used in the analyses was matched on disease variant and age at assessment visit. The possible impact on results of clinically relevant differences in factors such as age at disease onset (or predicted age) and genotype between the OTL-200 and the natural history group was not properly discussed and data were not presented to allow baseline comparison of the groups, which might have allayed such concerns.

The company did though present analyses using a subgroup of comparator patients who were untreated affected siblings of patients who received OTL-200; these untreated siblings would be expected to have the same genotype and a very similar age at disease onset. Although these analyses

should therefore be the most robust in terms of reducing concerns about bias, they were limited by both sample size (12 subjects treated with OTL-200 and 11 corresponding untreated siblings) and by the number of data points available for the untreated siblings.

3.2.4 Results of the OTL-200 studies

3.2.4.1 Summary of key trial outcomes

This section provides a summary of the key outcomes reported in the CS.

Given both the limited results data reported in the CS, and the small number of patients treated with OTL-200, the ERG requested that the company provide IPD for all patients. If these could not be provided the ERG requested a detailed summary of all outcomes in both OTL-200 treated patients and the natural history control group and a description of how the control group data were analysed, in order to further evaluate and validate results reported in the CS. The ERG also requested CSRs. The company did not provide the ERG with IPD, nor with CSRs. Although detailed summary results were provided for the OTL-200 cohort the lack of IPD, lack of detailed data on the comparator cohort and lack of useful baseline data for both cohorts meant the information available was inadequate for the ERG to properly evaluate the company's comparative analyses. These omissions meant that the EMA report ended up being a useful source of data.[2]

Overall, the ERG considers the results provided by the company to be incomplete. The results presented in this report are therefore based on both the results provided by the company and those reported in the EMA's EPAR. Where possible, efficacy results are presented for the indicated population dataset, i.e. [redacted] patients with PS-LI MLD, [redacted] patients with PS-EJ MLD and [redacted] patients with ES-EJ MLD (the latter subgroup was [redacted] patients in the CS). However, some of the graphs of individual patient results data were available only from the EPAR and only for patients in the registrational study 201222. [redacted]. Preliminary efficacy data from the six patients treated with the cryopreserved formulation are presented separately (Section 3.2.5).

Mean duration of follow up was [redacted] years for the PS-LI subgroup, [redacted] years for the PS-EJ subgroup and [redacted] years for the ES-EJ subgroup. Table 6 summarises the reported outcomes after 2- and 3-years' follow-up, comparing the OTL-200 treatment group to the natural history control group. The ERG notes some concerns with the analyses presented. Appropriate baseline data were not supplied for either the treatment or natural history group, therefore the ERG cannot confirm whether the groups were similar at baseline. Details of the statistical analyses performed were not reported. The most correct approach to analysing continuous outcomes would include adjustment for value at baseline, to

avoid bias due to variation in baseline values across patients or treatment groups; it does not appear that this was done. Analyses appear to have been adjusted for age at baseline only.

Table 6 Summary of key outcomes reported in the CS

Outcome	Subgroup	Intervention	N	Year 2			Year 3		
				Mean	Difference	95% CI or p-value	Mean	Difference	95% CI or p-value
GMFM total	Late Infantile	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-PS	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-ES	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
NCV Index	Late Infantile	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-PS	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-ES	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRI	Late Infantile	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-PS	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-ES	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
DQ	Late Infantile	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-PS	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Nat. history controls	[redacted]	[redacted]			[redacted]		
	Early Juvenile-ES	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Nat. history controls	[redacted]	[redacted]			[redacted]		

ES early-symptomatic, PS pre-symptomatic

In the Late Infantile patients, the results generally suggest that receiving OTL-200 retains both high motor function (GMFM mean [redacted] after 3 years) and cognitive ability (DQ mean [redacted] after 3 years). Untreated patients in the natural history group, by contrast, decline rapidly (GMFM mean [redacted]; DQ mean [redacted] after 3 years). This is sufficient to demonstrate evidence of a treatment benefit, even in this very small trial.

A similar benefit is also observed in the PS-EJ group with good physical and cognitive ability at 3 years (GMFM mean [redacted]; DQ mean [redacted]) also demonstrating evidence of a treatment benefit, although patients in the natural history arm appear to decline more slowly that for late infantile onset patients.

For patients in the early-symptomatic EJ group the pattern is broadly similar, although they have some physical, but not cognitive, decline at three years (GMFM mean [redacted]; DQ mean [redacted]), presumably because the patients had some physical symptoms prior to treatment. As for other groups, OTL-200 was generally statistically significant superior to the natural history group, but was not quite significant for GMFM after 2 years ([redacted]).

One possible area of concern is the MRI results in the ES-EJ group. MRI scores were substantially poorer (mean [redacted] after 3 years) than for LI or PS-EJ patients (mean after 3 years: [redacted] respectively), and OTL-200 did not achieve statistically significant superiority to the natural history group for MRI scores in the ES-EJ group.

The remainder of this section considers the key outcomes in more detail.

3.2.4.2 Gross Motor Function (GMFC-MLD)

The Gross Motor Function (GMFC-MLD) assessment levels range from normal (GMFC-MLD Level 0) to loss of all gross motor function (GMFC-MLD Level 6). Assessments can only be carried out from the age of 18 months onwards.

The CS provided reported very limited summary data on GMFC-MLD and did not formally compare the results for patients receiving OTL-200 to those in the natural history group. The ERG therefore considers analysis of GMFC-MLD using figures presented in the CS; reproduced here.

Figure 2 shows GMFC-MLD progression in Late Infantile patients. The ERG notes several concerns with the data here.

1. Several patients had GMFC-MLD levels of [redacted] at their first assessment timepoint, which does not fit with being pre-symptomatic at time of treatment. Most of these patients appear to have been recruited in the compassionate use programme. A possible explanation

for this is that these children had delayed onset of walking, so scores were lower, but they had no actual impairment

2. Follow-up time is short for many patients, with follow up only to age 3.
3. Several patients show declining GMFC-MLD levels over time. It is unclear whether these patients are experienced gradual long-term decline, or whether they will ultimately stabilise with some impairment.

Untreated siblings, however, show rapid decline in GMFC-MLD levels, all falling to [redacted]. The relative risk of being in GMFC-MLD Level 0 or 1 at age 4 is therefore approximately 10.05 (95% CI 1.45 to 69.67) in favour of OTL-200. Although this is a large relative risk, the ERG notes the extremely wide confidence interval, demonstrating the high uncertainty in results given the limited data.

Similarly, for the natural history group, the mean age of falling to Level 6 is around [redacted]. All patients in the natural history group appear to be in [redacted].

Figure 2 GMFC-MLD levels in Late Infantile patients

patients, at least some will experience decline over time. It is unclear whether such patients will ultimately stabilise with impairment, or will continue to decline until all physical function is lost. The situation is less clear for ES-EJ patients, given the limited numbers. Some may stabilise with impairment, but long-time decline may also be a possibility.

Table 7 Summary of trends in GMFC-MLD levels

Status	PS-LI	PS-EJ	ES-EJ
Stable at Level 0 – long term	[redacted]	[redacted]	[redacted]
Stable at Level 0 – short follow up	[redacted]	[redacted]	[redacted]
Stable at Level 1 or 2	[redacted]	[redacted]	[redacted]
Improving to Level 0 or 1	[redacted]	[redacted]	[redacted]
Declining to Level 5 or 6	[redacted]	[redacted]	[redacted]
Possible long-term decline	[redacted]	[redacted]	[redacted]
Possible long-term decline – limited follow up	[redacted]	[redacted]	[redacted]
Follow up too short to classify	[redacted]	[redacted]	[redacted]

Figure 3 GMFC-MLD levels in Early Juvenile patients (pre-symptomatic and symptomatic)

3.2.4.3 Gross Motor Function Measure (GMFM)

The CS did not report detailed by-patient information on GMFM scores. The ERG therefore uses data presented in the EPAR to consider the impact of OTL-200 on GMFM.[2]

Figure 4 shows the GMFM scores for the LI patients in the main trial (not including those in the expanded access scheme). The pattern of trends in GMFM scores is similar to GMFC-MLD. Most patients appear to stabilise at GMFM 80% or above, in line with normal development. Two show clear decline over time (one was excluded from CS analysis), and one had shorter follow up, with a possible decline. All show clear benefits of treatment compared to both untreated siblings and the natural history cohort, where GMFM scores are typically at or close to zero by age 6.

Table 8 summarises the trends in GMFM scores for all patients, including EJ patients and those in the expanded access scheme (from EPAR figures 13 to 16). The results suggest that for LI and PS-EJ patients most will stabilise at either 100% or at least 60%, although some will experience long-term decline. For ES-EJ patients all appear to experience decline in GMFM scores over time, although decline is slower than for untreated patients in the natural history cohort.

Figure 4 GMFM scores in Late Infantile patients (from EMA CHMP report)

Table 8 Summary of trends in GMFM scores

Status	LI	PS-EJ	ES-EJ
Stable at 100% long term	5	4	-
Rising in line with expected progression – short follow-up	2	1	-
Stable at 60-80%	4	-	-
Rising over time to around 80%	2	-	-
Declining	2 (1 excluded)	-	4 (1 excluded)
Possible long-term decline	-	1	1
Possible long-term decline – limited follow-up	1	-	1
Follow-up too short to classify	-	-	2 (excluded)

The EPAR also compared outcomes compared to those of healthy children. It reported that in the main study (201222), among the eight PS-LI subjects, four were within the range of gross motor function observed in a healthy cohort of children of similar chronological age throughout their follow-up and were consistent with the physiological progressive acquisition of new motor skills. The four PS-LI subjects who showed GMFM scores post-OTL-200 treatment below scores expected from the healthy cohort at a similar age all had abnormal neurological examination findings at baseline. Their results for ARSA activity in the CSF seemed similar to patients with better outcomes (Fig 10 of the EPAR). This further highlights the importance of treating as early as possible which was already

illustrated by the outcomes in the ES-EJ patients, most of which also had good ARSA activity in CSF responses.

3.2.4.4 NCV Index

Figure 6 (adapted from CS figures C27 – C29) shows the results of sequential Nerve Conduction Velocity (NCV) assessments in all patient groups. For late infantile patients, most patients had higher NCV Index scores than for the natural history population, suggesting that OTL-200 may reduce progressive peripheral neuropathy in some patients. However, scores are still well below the expected score for healthy children (a score of around 0). Three patients did not show any apparent benefit. Without IPD the ERG cannot determine with certainty which patients these were, but it is plausible that these included patients with declining physical function (from GMFC-MLD data).

Interpretation of the results from Early Juvenile patients is complicated by the very limited data. However, OTL-200 does not appear to improve peripheral neuropathy. Scores are, on average, worse for patients receiving OTL-200 than for patients in the natural history group, but are within the range of values in the natural history group.

To provide some insight regarding whether peripheral neuropathy might potentially be an issue in the longer-term, the ERG extracted data from the appendix document submitted by the company in response to the ERG's clarification questions. Figure 5 [redacted].

Figure 5 Mean NCV index in pre-symptomatic patients following treatment with OTL-200

3.2.4.5 Brain MRI total scores

Figure 7 (adapted from CS figures C24 – C26) shows the results of sequential MRI scans in all patient groups. For late infantile patients Brain MRI total scores are consistently low, and lower than all results from the natural history group. There is therefore reasonable evidence that OTL-200 materially improves MRI score in these patients. For PS-EJ patients MRI scores are generally below those in the natural history group, although with limited data. There is plausible evidence that OTL-200 materially improves MRI score.

For ES-EJ patients, Brain MRI total scores are below the average for the natural history group, but several are within the range seen in natural history patients. This is particularly the case if [redacted] is excluded. The ERG concludes that there is no convincing evidence that OTL-200 improves MRI scores in this group.

To provide some insight about whether slow demyelination of the CNS might potentially be an issue in the longer-term, the ERG extracted data from the appendix document submitted by the company in response to the ERG's clarification questions. [redacted].

3.2.4.6 Development Quotient

Figure 8 (adapted from CS figures C18 – C20) shows the results of Development Quotient (DQ) assessments in all patient groups. For late infantile patients DQ scores remain consistently [redacted]. By contrast all patients in the natural history group have declined to a score of [redacted]. High within-patient variability makes it difficult to assess whether patients are improving, declining or remaining stable over time. However, there seems to be good evidence that OTL-200 maintains high cognitive ability in late infantile patients.

For PS-EJ the pattern of data appears broadly the same, although with limited data. [redacted] of the patients may have declining DQ scores over time, after a period of initial increases, but they do not fall into regions representing cognitive impairment during their follow-up period.

For ES-EJ patients, [redacted]. Others remained consistently high, but substantial within-patient variation in DQ makes assessment of trends difficult.

Figure 6 NCV Index scores in the integrated data set (From CS figures C27-C29)

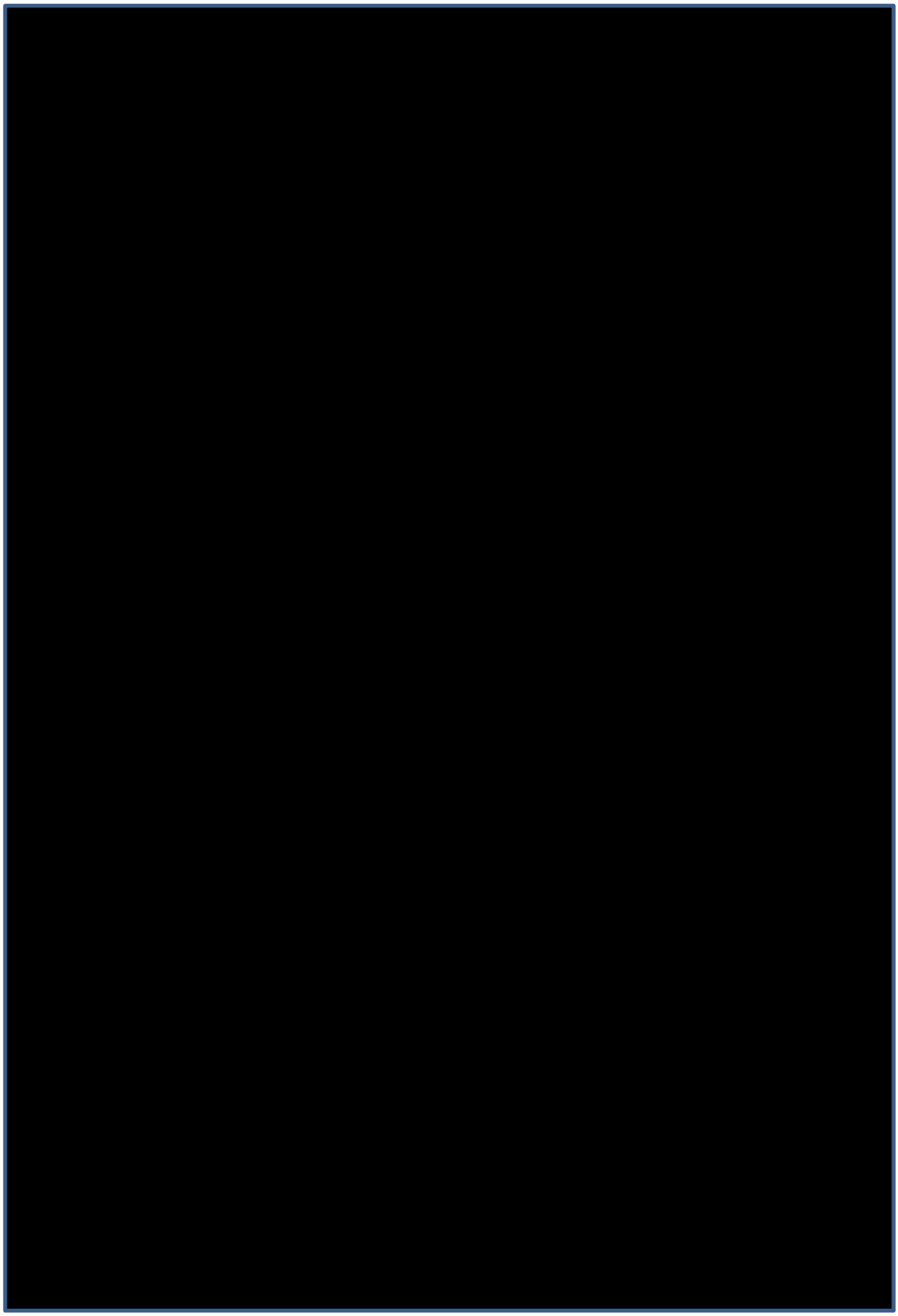


Figure 7 MRI scores in the integrated data set (From CS figures C24-C26)

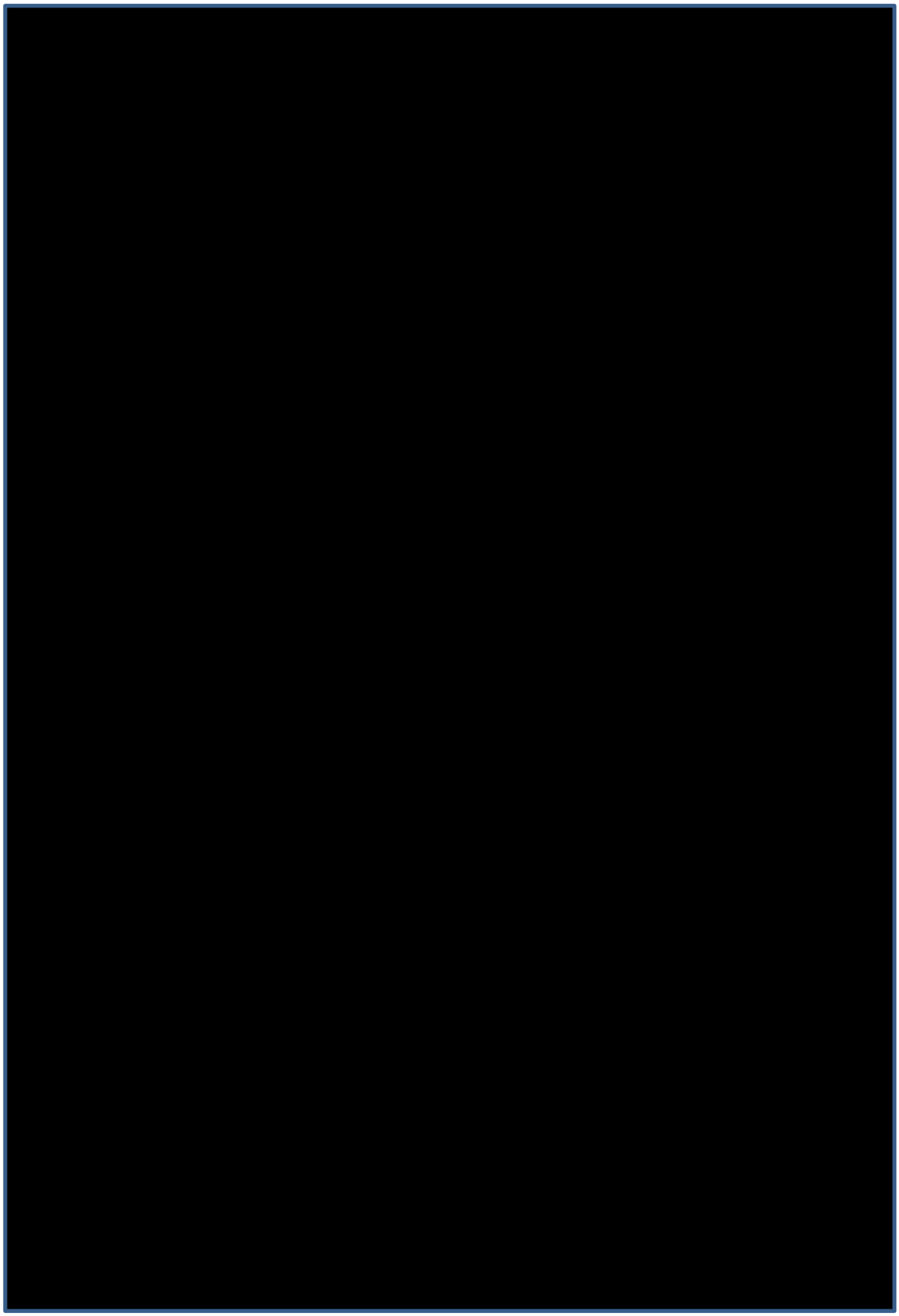


Figure 8 DQ in the integrated data set (From CS figures C18-C20)

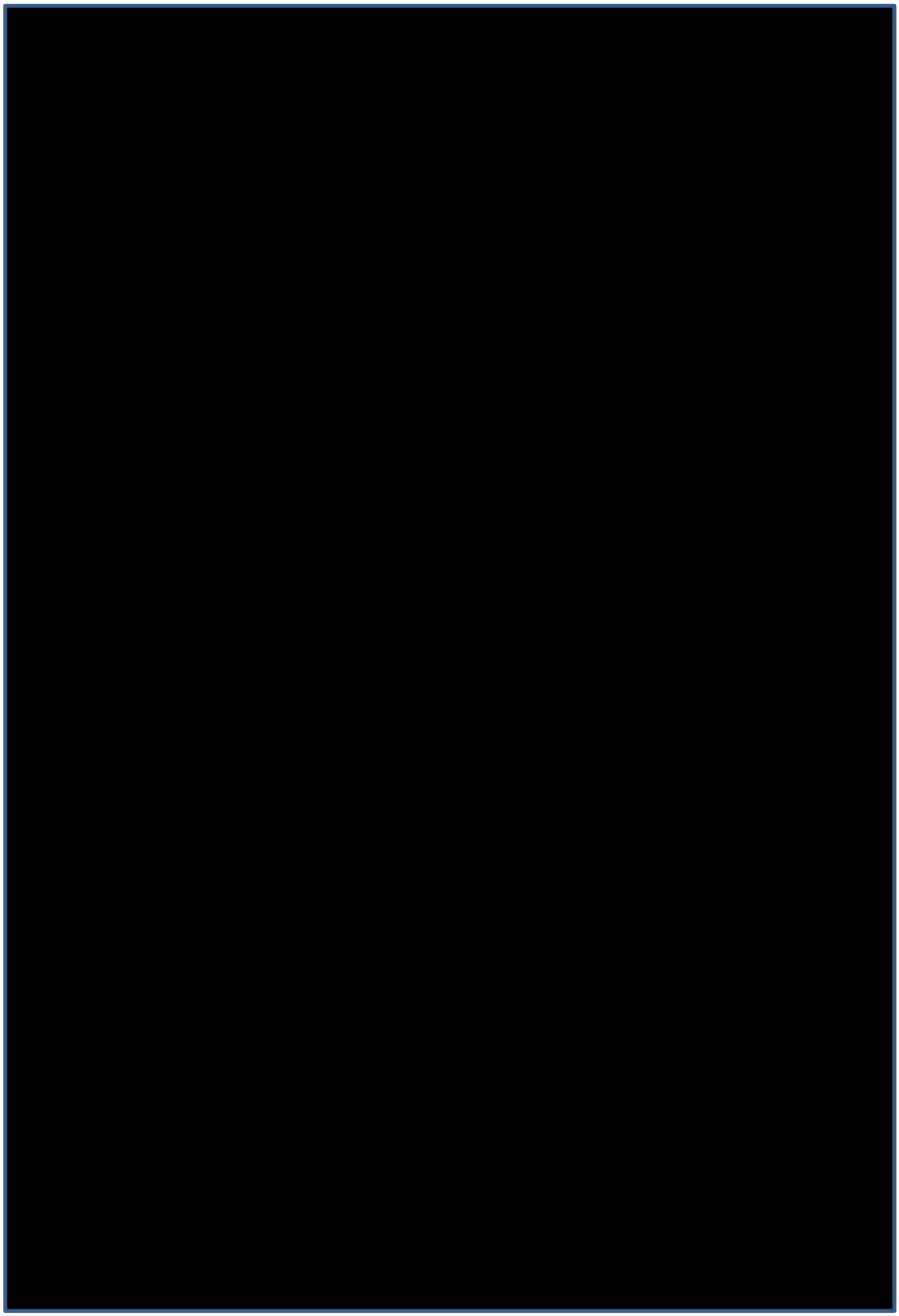


Figure 9 Brain MRI Total scores in pre-symptomatic patients following treatment with OTL-200

3.2.4.7 Survival outcomes

The CS reported survival analyses for overall survival, severe motor impairment-free survival (sMFS, defined as time to GMFC Level 5 or higher, or death), and severe cognitive and motor impairment-free survival (sCMFS, defined as time to both GMFC Level 5 or higher and DQ ≤ 55, or death). Comparisons were made between OTL-200 patients and both the natural history group and untreated siblings.

A summary of numbers of patients and the p-value from log rank tests reported in the CS is given in Table 9. The ERG notes that log rank tests are of limited value in interpreting survival outcomes as they produce only p-values, and not measures of difference between patient groups (such as hazard ratios). The ERG requested that the company provided Cox proportional hazards analyses, or similar, but the company declined to provide these. This, combined with the limited numbers of patients and events for each survival outcome, makes interpretation of these data difficult.

In late infantile patients, substantial differences in survival between OTL-200 patients and untreated siblings and the natural history group were observed. This is primarily because [redacted] occurred in the OTL-200 patients. The ERG notes that the CS analysis excludes the [redacted]. The Kaplan-Meier curves for late infantile patients compared to the natural history group are shown in Figure 10.

Results for early juvenile patients are less clear because of the very few patients and events in this group. There were too few deaths to draw any firm conclusions on overall survival. Results favoured OTL-200 for sMFS, but a single event was sufficient to move from [redacted] (for PS-EJ) to [redacted] (for ES-EJ), so log rank test analyses are not robust. Results also favoured OTL-

200 for sCMFS, however the ERG notes that this is primarily because [redacted]. Kaplan-Meier curves are not reported here on space grounds; they were presented in the CS (Figures C30 to C40).

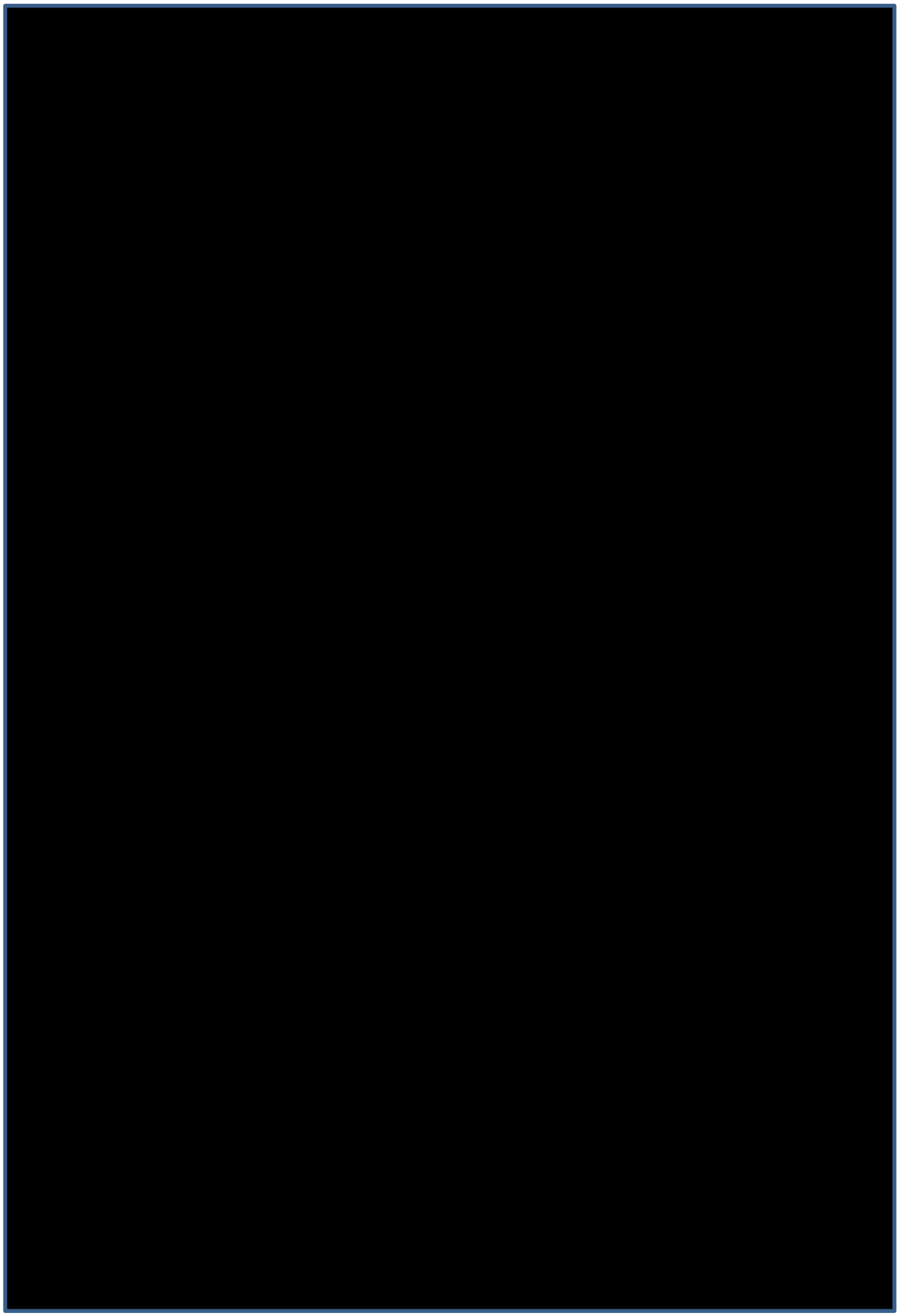
The ERG notes that by defining sMFS as GMFC level 5 or 6, patients with observed decline in GMFC Level (e.g. to Level 4) were classified as not having an event. Therefore, the apparent survival benefit from OTL-200 is at least partly due to the choice of outcome definition. Similarly, combining cognitive decline with physical function in sCFMS also favours OTL-200 because of the [redacted]. Without access to IPD, the ERG cannot determine if different outcome definitions would have led to different results.

Table 9 Summary of survival outcomes

Outcome	Subgroup	Intervention	Number of patients	Event-free at end of follow-up	Log rank test p-value
Overall survival	Late Infantile	OTL-200	[redacted]	[redacted]	
		Nat. history controls	[redacted]	[redacted]	[redacted]
		Siblings	[redacted]	[redacted]	[redacted]
	Early Juvenile pre-symptomatic	OTL-200	[redacted]	[redacted]	
		Nat. history controls	[redacted]	[redacted]	[redacted]
		Siblings	[redacted]	[redacted]	[redacted]
	Early Juvenile early-symptomatic	OTL-200	[redacted]	[redacted]	
		Nat. history controls	[redacted]		[redacted]
sMFS survival	Late Infantile	OTL-200	[redacted]	[redacted]	
		Nat. history controls	[redacted]	[redacted]	[redacted]
		Siblings	[redacted]	[redacted]	[redacted]
	Early Juvenile pre-symptomatic	OTL-200	[redacted]	[redacted]	
		Nat. history controls	[redacted]	[redacted]	[redacted]
		Siblings	[redacted]	[redacted]	[redacted]
	Early Juvenile early-symptomatic	OTL-200	[redacted]	[redacted]	
		Nat. history controls			[redacted]
sCMFS survival	Late Infantile	OTL-200	[redacted]	[redacted]	
		Nat. history controls	[redacted]	[redacted]	[redacted]
		Siblings	[redacted]	[redacted]	[redacted]
	Early Juvenile pre-symptomatic	OTL-200	[redacted]	[redacted]	
		Nat. history controls	[redacted]	[redacted]	[redacted]
		Siblings	[redacted]	[redacted]	[redacted]
	Early Juvenile early-symptomatic	OTL-200	[redacted]	[redacted]	
		Nat. history controls			[redacted]

* *Natural history group not distinguished between PS-EJ and ES-EJ in the CS*

Figure 10 Kaplan-Meier curves for overall, sMFS and sCMFS survival for late infantile patients



3.2.4.8 ARSA activity

Although ARSA activity is not an outcome of primary value to patients and parents, the ERG considers the results presented in the CS and EPAR here to highlight some concerns with ARSA activity over time.

Figure 11 shows ARSA activity in peripheral blood mononuclear cells (PBMC, from CS C11) and Figure 12shows ARSA activity in cerebrospinal fluid (CSF, from CS C12). In PBMCs ARSA activity rises rapidly and appears to remain stable over time. Levels are higher for Late Infantile patients than Early Juvenile patients, but there is insufficient data to determine if this is a meaningful difference. For ARSA activity in CSF the ERG notes the [redacted]. When asked to comment on this the company noted that ARSA levels remain within expected ranges for healthy adults (0.31 – 2.82 nmol/mg/h). The ERG notes that, if there is any further decline, levels would fall below that range. The company confirmed that the trial did not measure ARSA activity in CSF between months 60 and 90, so no further follow-up data are currently available.

In responses to clarification the company noted that there is no correlation between ARSA activity and motor function outcomes. However, the ERG notes that the data are too limited to confirm or refute any correlations between ARSA activity and motor function. The EPAR also explicitly states:

"*...that although the subjects performed better than subjects from the NHx cohort, deterioration was observed in motor function assessed by GMFM in pre-symptomatic LI-MLD subjects who had ARSA activity levels of 0.71nmol/mg/hr and 0.37nmol/mg/hr. Therefore, levels below 0.71nmol/mg/hr could be indicative for treatment effect*."

The ERG agrees with this conclusion, and therefore notes some concern that declining ARSA activity could be associated with decline in motor function over time.

Figure 11 ARSA activity in PBMCs

Figure 12 ARSA activity in CSF

3.2.5 Results using the cryopreserved formulation of OTL-200 (study 205756)

The OTL-200 results presented so far in this report relate to the fresh formulation. In clinical practice a cryopreserved formulation will be used. The company presented results from an ongoing small trial of patients taking the cryopreserved formulation (NCT03392987). The CS reported that none of the subjects had completed the primary endpoint (defined as completion of 24 months post-treatment) as

of the data-cut, so only preliminary data were presented (in Table C21 of the CS). The company also submitted IPD for the six included patients in an Appendix, following the ERG's request for more detailed data. Most of the results data related to four patients because one recently recruited patient had only baseline data and for another patient only 30 day follow up data were available. The mean follow-up was [redacted].

Given the immaturity of the available data and the very young patients studied (i.e. GMFM assessments can be inconclusive at such young ages) the most informative results at these early timepoints are the surrogate outcomes on ARSA activity. The results for ARSA activity in PBMCs (CS, Table C21) appear to be in line with those associated with patients taking the fresh formulation of OTL-200. Results for ARSA activity in the CSF were not reported in the CS but were made available in the appendix provided to the ERG at the clarification stage. The results for the four patients with follow up data beyond 30 days are presented in Table 10. Although ARSA levels in CSF [redacted]. In the remaining patients the levels either [redacted]. The lack of availability of IPD for patients receiving the fresh formulation makes direction comparison difficult. However, a graph provided in the clarification appendix (Figure 1.1.71), together with the EPAR graphs (which are available for some individual patients) suggest that ARSA levels typically peak at around 1 year after treatment in patients receiving the fresh formulation. In light of this the ERG has some concerns about the Table 10 results, especially given the EMA's observation that ARSA CSF levels above 0.71nmol/mg/hr may be needed to achieve a treatment effect in terms of GMFM stability (at least in LI patients). Longer-term data for these study 205756 patients, together with new data from more recently recruited patients are needed to allay concerns that the cryopreserved formulation may not be as effective as the fresh formulation.

Table 10 CSF ARSA activity in patients receiving the cryopreserved formulation of OTL-200

Timepoint	ARSA activity in CSF nmol/mg/h			
	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Day 90	[redacted]	[redacted]	[redacted]	[redacted]
6 Months	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]

ND Not detected, NA Not available

3.2.6 Comparator cohorts (natural history population)

3.2.6.1 Selection of comparator cohort and matching with the OTL-200 cohort

The ERG asked the company to clarify how the natural history (NHx) comparator group of MLD patients was selected. The company stated that the NHx patients selected for the matched analysis were defined as LI and EJ patients who had a study visit at which their chronological age fits within the range of ages for patients treated with OTL-200. Comparator patient data came from the OSR-TIGET study (n=31; 19 LI, 12 EJ) which has been enrolling patients since 2004; both prospective and retrospective data were used. In the OSR-TIGET study patients received best supportive care aimed at managing disease complications and maintaining the patient's quality of life. The company also stated that the natural history group used in the analyses comprised all of the eligible patients from OSR-TIGET that could reliably be included (i.e. individual patient matching was not performed). A matched sibling analysis was also undertaken but, as discussed earlier, the number of suitable patients was very small (12 patients treated with OTL-200 and 11 corresponding untreated siblings from the NHx Study).

As mentioned in section 3.2.3, the ERG thought that consideration of the impact of confounding between the population receiving OTL-200 and the age and disease variant-matched natural history population (the main comparator group) was not well presented or discussed in the CS. The company's *Summary of clinical efficacy* document[6] reported that in 2009, GlaxoSmithKline received advice from the EMA's Committee for Medicinal Products for Human Use that indicated subjects in the NHx study would provide an acceptable comparator group for Study 201222, provided they were similar to the OTL-200 treated subjects with respect to age, genotype, and disease stage. The company reported using age and disease variant-matching in its submission. Table and figure footnotes in the CS mention the use of ANCOVA, but with adjustment only for age (at assessment). Genotype was also mentioned but only in the company's *Summary of clinical efficacy* document.[6]

The ERG considers that age at disease onset (or predicted age) should be an important prognostic characteristic to consider in any MLD patient matching exercise, especially given that the ERG's clinical adviser described the disease variants in MLD as being part of a spectrum, rather than fixed categorisations. Although the ERG requested baseline data on many specific characteristics to allow comparison of the OTL-200 and comparator cohorts the company did not provide them. The lack of a detailed explanation of exactly how the comparator cohort data were analysed compared to the OTL-200 data, together with lack of key baseline data for both cohorts is a serious flaw in the submission. It is unclear how well-matched the two cohorts are and whether or not matching on genotype was performed, as suggested by the EMA. In light of this the effect estimates for comparisons between the OTL-200 and comparator cohorts should be judged as having a very high risk of bias.

3.2.6.2 Exclusion of patients who received HSCT from the comparator cohort

As discussed in section 2.3.3, the ERG thinks that HSCT should not have been excluded as a comparator as it may be considered as a treatment option for some patients. The ERG's clinical adviser thought that although its use may be limited in the NHS, it would still sometimes be offered as a palliative option in the context of someone diagnosed very early. Patients would have to be pre-symptomatic and without neurological symptoms. It appears that clinical practice on the use of HSCT in the NHS varies from centre to centre. The ERG's clinical adviser estimated that HSCT (preferably using umbilical cord blood transplantation) might be offered to half of all truly asymptomatic patients and about half of those might proceed to HSCT. Patients with an EJ sibling might be expected to have better outcomes. To get some idea of outcomes following HSCT the ERG identified studies in the systematic review report submitted by the company which reported data on GMFC-MLD outcomes categorised by GMFC-MLD level at baseline (before HSCT). The results for patients with GMFC-MLD levels of 0 or 1 (i.e. one of the key criteria needed for treatment with OTL-200) are presented in Table 11. Of the nine patients with GMFC-MLD level 0 at baseline four appear to show a clear benefit, four follow a decline similar to natural history and one died as a result of HSCT treatment. Of the six patients with GMFC-MLD level 1 at baseline three appear to show a clear benefit, and three follow a decline similar to natural history. Although these data do not relate to UK patients they nevertheless suggest that HSCT may sometimes be considered as a viable option which may improve GMFC-MLD level outcomes in pre- and early-symptomatic patients, especially early-juvenile patients. The ERG therefore concludes that the removal from the appraisal of HSCT as a comparator treatment is likely to overestimate the efficacy of OTL-200 when compared to comparator patients.

. Following a ERG clarification question on HSCT the company informed the ERG that one patient who had received HSCT had been included on the NHx comparator cohort. This patient had a poor outcome following HSCT having "*…experienced engraftment failure around 6 months after the HSCT transplantation and subsequently experienced rapid decline in cognitive and motor function…*". This suggests that the company has been inconsistent in its approach to HSCT. The lack of clear inclusion and exclusion criteria in the submission for the NHx cohort together with the company not providing access to clinical study reports (which were requested by the ERG) hampered the ERG's appraisal of the validity comparator cohort.

Table 11: IPD from published studies reporting GMFC-MLD outcomes after HSCT

Patient ID, year of HSCT	Age^	MRI score^ or finding	GMFC-MLD Outcome
Groeschel et al 2016[3]			
GMFC-MLD level 0 at HSCT			
12, 2002	4.6	-	Stabilisation: Remains pre-symptomatic and at level 0, 12.6 years after HSCT
13, 2007	4.2	12	Progression: to level 6, 5.2 years after HSCT
14, 2007	4.2	13	Progression: to level 6, 5.2 years after HSCT

19, 2004*	4.8	7	Stabilisation: dropped to level 1 0.8 years after 2nd HSCT, remaining at level 1 for around 8 years.
23, 2006	5.4	0	Stabilisation: dropped to level 1 3.9 years after HSCT remaining so for over 3 years
24, 2010**	1.6	0	Treatment-related death shortly after 3rd HSCT
GMFC-MLD level 1 at HSCT			
1, 2001	4.9	14	Stabilisation: Dropped to level 2 around age 14.9. Remained at level 2, 13.5 years after HSCT
2, 2009	6.0	17	Stabilisation: Remains at level 1, 5 years post-HSCT
15, 2008	3.8	19	Progression: Dropped to level 5, 3.8 years after HSCT
Boucher et al 2015[8]			
GMFC-MLD level 0 at HSCT			
2, 2004	0.3	No abnormality	Progression: Dropped to level 4 around 2 years after HSCT
3, 1995	0.4	Abnormality	Progression: Dropped to level 6 around 1 year after HSCT
8, 1994	3.4	Abnormality	Progression: Dropped to level 2 around 10 years after HSCT
GMFC-MLD level 1 at HSCT			
4, 1984	4.8	No data	Progression: Dropped to level 6 around 20 years after HSCT
9, 2001	4.2	Abnormality	Progression: Dropped to level 6 around 3 years after HSCT
10, 1996	5.7	Abnormality	Progression: Dropped to level 5 around 3 years after HSCT

^ At HSCT, Age in years, *patient had 2 HSCTs, ** patient had 3 HSCTs

3.3 Adverse events

The CS provided a summary of adverse and serious adverse events reported in the [redacted] patients in the integrated data set, and for the [redacted] patients in the cryopreserved formula trial (Study 205756). As noted elsewhere, the company declined to provide IPD on adverse events, and did not provide any further data at time of clarification. As far as the ERG could determine, adverse event data were not reported in any of the supplied supplementary material, so the ERG cannot verify the accuracy of the adverse event data reported in the CS.

No adverse event data were supplied for untreated siblings, or the untreated comparator group more generally. Therefore, the ERG cannot compare the reported adverse events to an untreated group and cannot determine whether events are more or less common among patients treated with OTL-200. Events were pooled across all patients, and did not distinguish between late infantile and early juvenile groups. The ERG cannot therefore determine whether adverse event rates vary with type of patient.

As a broad conclusion, the CS claimed that "safety findings following treatment with OTL-200 are consistent with what would be expected in patients with MLD and who have undergone busulfan conditioning and subsequent haematological reconstitution". The ERG cannot confirm this due to absence of data on the historical control group.

Table 12 (adapted from CS Tables 25 and 26) summarises the reported adverse events in the 29 patients in the integrated data set. The most common specific adverse events were febrile neutropenia (79% of patients), gait disturbance (52%) and stomatitis (41%). Adverse events were more common in symptomatic patients than in pre-symptomatic patients, particularly during the treatment phase.

Renal tubular acidosis or metabolic acidosis occurred in 19 patients, but most were in the pre-treatment phase. Sixteen patients experienced hepatobiliary AEs during follow-up. Four patients experience Grade 2 adverse drug reactions associated with OTL-200 treatment.

Table 12 Summary of adverse events in integrated data set (from CS Tables 25 and 26)

Period	Event type	Number in pre-symptomatic patients (n=20)		Number in symptomatic patients (n=9)	
		Patients	Events	Patients	Events
Pre-treatment	AE	20	55	9	24
	SAE	2	10	0	0
Treatment phase	AE	9	12	8	11
Post-treatment	AE	20	321	9	144
	AE related to MLD	-	24	-	49
	Treatment-related AE	4	20	0	0
	AE and withdrawal	1	5	2	2
	SAE	14	70	6	17
	Treatment-related SAE	0	0	0	0
	Death	1	-	2	-

3.3.1 Serious adverse events

Twenty patients experienced an SAE, most were gastrointestinal disorders, infections and infestations, or nervous system disorders. Four patients experienced device-related infection SAEs. Two patients had SAEs related to metabolic acidosis that resolved with treatment.

The CS claimed that none of the SAEs were treatment-related and were instead related to myeloablative conditioning with busulfan and to the background disease. The ERG cannot confirm this due to absence of data on the historical control group, but notes that conditioning is required as part of the treatment process. The ERG considers that such SAEs should be assumed to be treatment related.

3.3.2 Deaths

Of the three deaths, two occurred in patients with rapid disease progression. These patients were described as being not be eligible for treatment in the post-market authorisation in the CS. [redacted]

[redacted]. The ERG notes that patients could potentially deteriorate between identification and treatment, so initiating treatment before disease progression may be essential.

The third death [redacted]. It was deemed to be unrelated to OTL-200 nor to MLD. The ERG's clinical adviser considered this to be a reasonable assessment.

3.3.3 Cryopreserved formulation patients

The CS summarised the AEs experience by patients receiving the cryopreserved formulation of OTL-200 (Study 205756). All [redacted] patients experienced at least one AE; 3 patients during the treatment phase and 5 during follow-up (see CS Table C24). Most AEs were gastrointestinal disorders, hepatobiliary disorders or infections or infestations. The company could not assess whether these events were related to OTL-200 treatment, however the CS stated that they were expected for patients who undergo conditioning or are suffering from MLD. Rates of adverse events appeared consistent with the main integrated data set, but patient numbers are too small to draw any firm conclusions as to whether the adverse event rates with the cryopreserved formulation differ from when using the fresh formulation.

3.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS presented no direct or indirect comparison of OTL-200 with any other active intervention, on the grounds that no suitable intervention for patients with late infantile or early juvenile MLD exists because HSCT would not be used in these patients. As discussed in Section 2.3.3, the ERG questions that assumption and HSCT may be used in some patients, and so should have been considered in direct or indirect comparisons with OTL-200.

3.5 Critique of the indirect comparison and/or multiple treatment comparison

As stated in Section 3.4, no indirect comparison of OTL-200 with any other intervention was performed.

3.6 Additional work on clinical effectiveness undertaken by the ERG

The company declined to supply IPD, as requested by the ERG, or to supply complete summary trial data (such as adequate baseline data and full clinical study reports). Therefore, the ERG was unable to carry out any further analysis or investigation of the trial data.

3.7 Conclusions of the clinical effectiveness section

3.7.1 Quality and completeness of the OTL-200 trial data

The ERG understood that limited evidence would be available in this appraisal, given the nature and rarity of the condition being assessed. Nevertheless, in the company's submission, data were often limited in detail and the reporting of specific methods was sometimes sparse. Of particular note, the baseline data for both cohorts was inadequately reported, despite the ERG requesting data on a specific list baseline characteristics. Given the very small cohort, an understanding of how outcomes changed over time in individual patients would have been helpful, but the company did not provide IPD. Given these limitations, the ERG found the EMA's EPAR report to be a useful supplementary source of data. Few details were reported on the methods used for matching and analysis when comparing the OTL-200 and untreated cohorts; the implications of this was exacerbated by the lack of baseline data. Clinical study reports (CSRs) requested by the ERG were not provided by the company. Interpretation of the submitted results data by the ERG was therefore difficult and there is considerable uncertainty in the accuracy and reliability of the treatment effect estimates.

3.7.2 Effectiveness in Late Infantile patients

The evidence on the effectiveness of OTL-200 was most substantial in patients with late infantile onset of MLD. However, the ERG notes that only [redacted] such patients received OTL-200, some with limited follow-up.

OTL-200 appeared to preserve motor function in these patients, with most remaining at GLMC-MLD Level 0 or 1 throughout follow up. By contrast, untreated siblings and patients in the untreated natural history cohort showed rapid decline in motor function. The ERG notes that 3 patients showed some signs of deterioration in motor function during follow-up; it is unclear whether these patients will continue to decline or will stabilise with some impairment.

Patients treated with OTL-200 appeared to maintain good cognitive function, based on DQ scores, although high within-patient variability limited the scope to analyse the data. Untreated siblings and patients in the untreated natural history cohort showed rapid decline in cognitive function. Other outcomes, including MRI scores, also suggested a benefit of OTL-200.

The ERG notes two possible concerns:

1. Patients still appear to experience peripheral neuropathy (from NCV Index scores), although potentially slightly less than for untreated patients.

2. ARSA activity in CSF declined for several patients from 24 months onwards. It is currently unclear whether this will continue to decline, or what impact it might have on functional outcomes.

3.7.3 Effectiveness in Pre-symptomatic Early Juvenile patients

The evidence on the effectiveness of OTL-200 was very limited in patients with pre-symptomatic early juvenile onset of MLD, with only [redacted] such patients receiving OTL-200, one with very limited follow-up.

As for LI patients, OTL-200 appeared to preserve motor function in these patients, although one showed possible beginnings of decline, and one had too little data to make an assessment. Patients showed no evidence of cognitive decline. Patients in the untreated natural history cohort showed rapid decline in motor and cognitive function, although slower than for LI patients.

For other outcomes, data were generally too limited to draw any clear conclusions. NCV Index scores were similar to those in untreated patients, suggesting that OTL-200 does not improve peripheral neuropathy.

3.7.4 Effectiveness in Early-symptomatic Early Juvenile patients

The evidence on the effectiveness of OTL-200 was very limited in patients with early-symptomatic early juvenile onset of MLD, with only [redacted] such patients receiving OTL-200, plus one that the ERG considers to have been incorrectly excluded from analysis. Interpretation of the data is complicated by substantial heterogeneity across patients, particularly in age at treatment.

All patients with sufficient follow-up data showed at least possible decline in gross motor function so it is unclear, without longer follow-up, whether patients will stabilise with impairment or continue to decline. Only one patient experienced cognitive decline, but data were too limited to reach firm conclusions on cognition. For other outcomes data were generally too limited to draw any clear conclusions. NCV Index scores were similar to those in untreated patients, suggesting that OTL-200 does not improve peripheral neuropathy.

3.7.5 Cryopreserved formulation

Given the size of the cohort ([redacted]) and the immaturity of the available data on the cryopreserved formulation (the formulation which will be used in clinical practice) the most informative results are the surrogate outcomes on ARSA activity. The ERG identified that most of the patients receiving the cryopreserved formulation had stable or declining ARSA activity in the CSF after 6 months, in contrast to improving ARSA activity over that period in patients receiving the fresh formulation. Due

to limited data and follow-up, it is therefore currently unclear whether this represents a genuine difference in CSF ARSA activity between formulations.

3.7.6 Key issues

The ERG notes the following key concerns with the clinical effectiveness evidence for OTL-200:

1. Substantial limitations with the data supplied restricted the ability of the ERG to assess OTL-200.
    - This includes lack of baseline data for both cohorts and limited outcome data and methods of analysis details for the natural history cohort.
    - The ERG's request for IPD was declined and clinical study reports were not provided, despite being requested.
2. Potential for long-term decline in motor function in some patients
    - Some patients showed decline in motor function; it is unclear whether these patients will stabilise with impairment or continue to decline.
    - This is particularly an issue for ES-EJ patients.
3. Decline in ARSA activity in CSF
    - This was observed for LI patients after 24 months. It is currently unclear if this decline will continue, and whether it will impact on functional outcomes.
4. Patients receiving OTL-200 still experience peripheral neuropathy
    - For early juvenile patients NCV Index scores were as bad or worse as those in untreated patients
    - It is unclear what long-term impact this might have on long-term health or quality of life
5. ARSA CSF activity using cryopreserved formulation may be inferior to fresh formulation
    - Data currently too limited to assess whether this is a real or a chance finding
    - Follow-up data too immature to properly assess impact on functional outcomes

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

4.1.1 Searches

The company implemented a broad search strategy to identify studies on both the clinical and cost-effectiveness of OTL-200. The searches have been critiqued previously in Section 3.1.1.

4.1.2 Inclusion/exclusion criteria used for study selection

The company applied eligibility criteria as outlined in Table D1 of the CS to the results of the broad search strategy in order to identify studies relevant to the economic evaluation. The company sought to identify studies on cost-effectiveness, health related quality of life, and cost and resource use associated with OTL-200. The company stated in their inclusion criteria that searches were not limited by language, but it was not clear whether non-English language studies were considered eligible for inclusion in the review.

4.1.3 Studies identified in the review

The database searches identified a total of 8,983, of which 148 were selected for full-text assessment based on screening of titles and abstracts. A total of 146 studies were excluded for the reasons summarised in the PRISMA flow diagram (CS Figure D1), with only two studies meeting the review inclusion criteria. The review identified no existing cost-effectiveness models of any design.

The two studies included in the review examined the burden of MLD on caregivers (Pang *et al*. 2020[9], and Eichler *et al*., 2016[10]). The company stated that one study included utility estimates for caregivers, and resource use information was identified only in Pang *et al*.,[9] which reported indirect carer costs. Neither study was considered relevant for use in the company's cost-effectiveness analysis.

4.1.4 Conclusions of the cost-effectiveness review

Given the limited availability of OTL-200 and The ERG considers it likely that the cost-effectiveness review as implemented by the company will have captured all potentially relevant economic evidence on OTL-200. The most relevant source of evidence to address the present decision problem is therefore the *de novo* cost-effectiveness analysis reported in the CS.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 13 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 13 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Heath effects from both patients and carers were included.
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model had a life-time horizon of 100 years. No patients were expected to be alive beyond this period.
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Partial. The utility study elicited utilities for all health states was based on time trade off (TTO) exercise which was used to generate utilities. EQ-5D was not used.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, utilities applied to health states were elicited using vignettes describing each health state.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Utilities were elicited directly from 101 members of the public.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No, costs and benefits have been discounted at 1.5% per annum in the base case analysis. A 3.5% discount

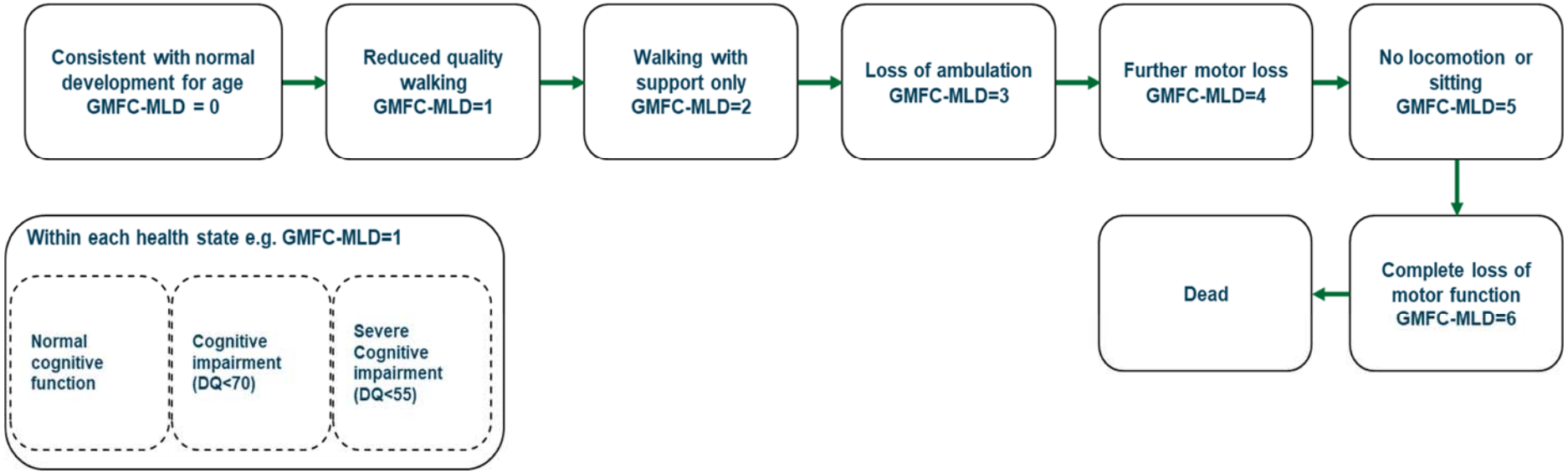
		rate is explored in scenario analyses provided at the clarification step.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Overview of approach

The company developed a de novo economic analysis to appraise the cost and benefits of OTL-200 for the treatment of MLD in pre-symptomatic late infantile, pre-symptomatic early juvenile, and early symptomatic early juvenile patients. The model compares OTL-200 with best supportive care (BSC) consisting of palliative supportive care. The company submission is based on a multi-state Markov model approximating a partition survival model whereby patients move through a set of exhaustive and mutually exclusive health states. The model structure adopted consists of eight health states (inclusive of death), which characterise the progression of MLD patients over the course of the model's time horizon, see Figure 13. The eight health states included in the model were defined according to the GMFC-MLD clinical rating scale, which is a validated measure designed to assess gross motor function in patients with MLD. A GMFC score of zero reflects patients who have not yet experienced motor function decline and are still developing in line with a broad range of normal development. Scores of 1 to 6 reflect clinical manifestations of the disease, with higher scores denoting increasing loss of motor function, such that a score of 5 indicates near complete loss of locomotion and sitting without support, and 6 denotes a state of complete loss of motor function, see Table C10 of the CS for a full description of scores.

Figure 13 Model Schematic (reproduced from the CS, Figure D2)



4.2.2.2 Cognitive sub-states

To reflect the fact the MLD impacts upon cognitive as well motor function, patients in each of the GMFC health states were classified into one of three cognitive function sub-states: Normal/mild loss of cognition (DQ>70); moderate impairment (70 > DQ > 55); and, severe impairment DQ<55). The cognitive sub-states were used to apply sub-state specific utility values to each GMFC-MLD stage but had no impact on either costs or survival. In the original company base-case the cognitive sub-states were only applied once children reached 48 months of age. This was justified on the basis that cognitive decline is highly predictable in LI patients, and accompanies deterioration of gross motor function in a more consistent way. See Section **Error! Reference source not found.** for further discussion.

In the company's model, the distribution of patients across the cognitive sub-states is treatment dependent and is summarised in Table 14. In the BSC arm the proportion of children with moderate and severe impairment was drawn from a clinical elicitation exercise and modelled such that cognitive decline broadly aligned with loss of gross motor function. In contrast, in the OTL-200 arm of the model it was assumed that loss of gross motor function would not necessarily be accompanied by loss of cognitive function. As a result, it was assumed that most OTL-200 patients remain in the normal/mild loss sub-state until they reach GMFC 5, see Table 14. The company cited clinical opinion in support of the assumption that cognitive function would be preserved despite progression of motor dysfunction, however, the ERG could not verify the source of this position in the elicitation report provided and requested that the company provide justification for this assumption at the clarification step (Question B21). The company's response highlighted evidence from the integrated efficacy analysis suggesting that patients receiving OTL-200 had largely retained normal or near-normal cognitive function, while over a similar time frame, patients in the OSR-TIGET natural history cohort experienced a significant decline in cognitive function.

Table 14 Cognitive sub-state distribution by GMFC-MLD stage (adapted from CS Appendix Table D4 and D5)

	Best supportive Care			OTL-200		
Cognitive Sub-state distribution	**Normal/mild impairment**	**Moderate Impairment**	**Severe Impairment**	**Normal/mild impairment**	**Moderate Impairment**	**Severe Impairment**
GMFC-MLD 0*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GMFC-MLD 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Value only applied after 12 months. Prior to this, patients have baseline values applied.

The ERG has substantial concerns regarding the evidence provided to support the application of differential assumptions for OTL-200 patients, and notes that these tend to strongly favour OTL-200 given the punitive utility decrements applied in the moderate and severe impairment sub-states. The evidence provided by the company providing a direct comparison of the rate of cognitive decline in OTL-200 patients with the OSR-TIGET natural history cohort is not informative in terms of justifying differential application of the cognitive sub-states. It is accepted that OTL-200 is an effective treatment and can help delay progression of disease, but to demonstrate that OTL-200 preserves normal cognitive function in patients whose motor function has declined, a conditional analysis by GMFC score is required. The use of broad DQ categories in which patients with normal cognitive function are grouped with those with mild cognitive impairment also serves to partially obfuscate decline observed in some patients, with data provided at the clarification step suggesting that 2/6 (33%) of patients in the LI cohort had experienced mild cognitive impairment at 3 years.

Importantly, the ERG considers there to be substantial uncertainty regarding the biological rationale for these assumptions. Advice received from the ERG's clinical advisor suggested that this could be possible if the protective effect of OTL-200 is more rapidly established in the brain, but progression continues in the central and peripheral nervous system. Experience of the pattern of decline in patients treated with HSCT and limited evidence of peripheral neuropathy in OTL-200 trials suggest this may be a possibility, but the evidence is far from conclusive, and is not supported by evidence of ARSA activity in the PMBC, see Figure 11. Further evidence on ARSA activity in the CNS, shown in Table 15, demonstrates that CSF ARSA activity in partial responders did not reach the normal reference range in all patients until at least two years after treatment, and was only [redacted] at 6 months. By contrast, [redacted] of partial responders achieved normal levels of ARSA activity by 6 months in the PBMC, and [redacted] at 1 year. This is inconsistent with the company's model of the mode of action of

OTL-200, as an immediate halt of cognitive decline would require a rapid establishment of supraphysiological levels of CSF ARSA activity in the CNS and brain. Given this uncertainty the ERG considers there to be insufficient evidence to support the assumption that OTL-200 will have an independent and ostensibly stronger treatment effect upon the brain than the wider CNS. The ERG therefore explores alternative scenarios in Section 6.

Table 15 Percentage of subjects within or above normal reference range for ARSA in CSF by response status (Reproduced from clarification response Table B6)

CSF	Overall (N=[redacted])	Full responder (N=[redacted])	Partial responder (N=[redacted])
6 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

4.2.2.3 Modelling of standard care

Patients modelled to receive best supportive care are assumed to progress through each of the GMFC health states until they reach the final 'alive' health state GMFC 6. Upon entering this health state, all patients are assumed to die due to their disease or related complications. The majority of patients in the untreated cohort are therefore assumed to die from their disease; a small minority are assumed to die from other causes in line with general population mortality applied in all health states. Transition probabilities between states were based on the OSR-TIGET natural history cohort, see Section 4.2.7.2 for details.

The ERG is generally satisfied with the modelling of BSC, but notes the use of a Markov model leads to predictions that do not align with the natural history data. This is due to the "memoryless" nature of Markov models which means that previous transitions have no impact on future transitions. In the context of the current model, this feature combined with the relative short cycle length, means that some patients progress through the model very quickly. For example, it is possible for patients to transition from GMFC 0 to GMFC 6 in just 6 months. Equally the model structure implies that a non-negligible proportion of patients are predicted to be alive into their 20s and 30s; this is extremely unlikely in the real world given the known natural course of these variants of MLD. It is difficult to ascertain the impact of these limitations on the results. Model results are primarily determined by mean time in state which can be modelled accurately using a Markov model (note calculations errors meant this wasn't the case in the company's base analysis). The mistiming of events, however means that discounting and other age/time related features of the model will not be estimated correctly which will impact on model results. To address this issue the ERG requested that company consider alternative approaches to modelling time in state, and in particular survival time in GMFC 6 (Question B9). This was implemented by the company as part of their clarification response and is further detailed in Section 4.2.7.3.

4.2.2.4 Modelling of OTL-200 treatment response

To capture the benefits of treatment, patients receiving OTL-200 were classified as either full responders, stabilised partial responders, or unstable partial responders. Each category is associated with specific alternative symptom trajectory expressed in terms of assumed transitions between GMFC health states. The assumptions associated with each trajectory and the proportion of patients within each category are central to the calculation of the health benefits and costs associated with OTL-200. A detailed review of each category is therefore presented considering the assumptions made and how these relate to the clinical evidence and mechanism of action of OTL-200.

Full response: Full responders were assumed to represent patients treated prior to symptom onset, and who then remained symptomatically stable with motor and cognitive function fully intact. In the context of the model, these patients were assumed to remain in the GMFC 0 health state for the full-time horizon and lead normal healthy lives in line with the general population. This was reflected in the Health related quality of life (HRQoL), costs and mortality rates applied in the GMFC 0 health state.

The ERG recognises the conceptual and biological rationale for the full responder category but has concerns that a focus on GMFC category trial outcomes may be overly simplistic and fail to capture more subtle manifestations of the disease beyond GMFC category. One example of this is progressive peripheral neuropathy, which as outlined in Section 3.2.4.4 was noted in many patients receiving OTL-200. The symptoms of peripheral neuropathy, which may include clumsiness, muscle weakness, sensory deficits and areflexia, would, however, not necessarily be reflected in GMFC scores which focus principally on the ability of an individual to walk and sit up. Stability in terms of gross motor function (GMFM) total score appeared more ambiguous. Similarly, other surrogate markers of disease including MRI scores and NCV scores, all show some evidence of disease progression amongst patients classified as full responders.

Myeloablative conditioning, required as part of the administration of OTL-200, is also associated with significant long-term adverse effects including dental problems (98.4%), short stature (75.4%), cognitive deficits (70.5%), and pulmonary dysfunction (25%).[11] The characterisation of full response as normal general population health may therefore be inappropriate and may serve to overestimate the benefits of OTL-200.

*Partial response: All p*atients not considered full responders were classified as partial responders, which comprised two distinct groups. The first, stabilised partial responders, consists of patients who are either treated after symptom onset (GMFC>0) and subsequently stabilise, or patients who continue to experience some progression of disease following treatment but subsequently stabilised. The assumption of continued decline followed by stabilisation was based on clinical opinion, and the

GMFC trajectories observed in some OTL-200 patients. In the original company base-case, all stabilised partial responders were assumed to stabilise in GMFC 2. However, clinical advice received by the company suggested that patients may stabilise at any point up to GMFC 4. In response to the ERG's clarification questions, the model structure was altered to allow late stabilisation across a range of GMFC stages, with the revised base-case assuming that patients will stabilise in either GMFC 1 or GMFC 2 (see Table 16).

Table 16 Modelling of partial responders in company base-case (adapted from company executable model)

	Partial response (OTL-200 trial)	Stage at stabilisation (% of partial responders)	
		GMFC 1 (%)	GMFC 2 (%)
Pre-symptomatic late infantile	[redacted]	[redacted]	[redacted]
Pre-symptomatic early juvenile	[redacted]	[redacted]	[redacted]
Early-symptomatic early juvenile	[redacted]	[redacted]	[redacted]

The second sub-group of partial responders comprises patients in whom treatment with OTL-200 has failed to stabilise the progression of symptoms. These patients are assumed to continue to progress through each of the GMFC health states in a similar way to standard care patients, but at a slower rate. These patients are henceforth referred to as unstable partial responders. Similar to untreated patients, once partial responders (unstable) reach the final GMFC health state (GMFC 6) it assumed they will die as a result of either the condition or related complications. Classification of patients into each of the response categories and subsequent assumptions about stabilisation and rate of progression were based on a combination of data from the OTL-200 integrated analysis and clinical opinion, see Section 4.2.7.1 for comprehensive overview and critique.

The ERG is concerned about the validity of the distinction between stable and unstable partial responders and the connected assumption that all pre-symptomatic stabilised patients will stabilise in a GMFC score of 1 or 2. In the OTL-200 trials there appeared to be few patients who would meet the criteria for being a stabilised partial responder (initial decline followed by long-term stabilisation). Equally, there is limited evidence on unstable partial responders as the limited follow-up means that is uncertain whether all patients who have dropped below a GMFC of 2 score will continue to decline or whether they will subsequently stabilise with lower scores.

The company's justification for the suggested trajectories provided at the clarification stage (Question B1) highlighted that the modelled trajectories were based on their understanding of the mechanism of action of OTL-200. The company noted that once OTL-200 is administered to the patient, the treatment effect will only become apparent after the corrected cells have engrafted in the

haematopoietic compartment, migrated to the CNS, and begun delivering enough enzyme to the surrounding cells to prevent further sulfatide accumulation. Variation in the time over which this process occurs results in variability in the benefits patients experience from treatment, and is dependent upon the underlying rate of progression and the point at which patients are treated.

The ERG accepts the biological rationale for late stabilisation put forward by the company and considers that it aligns with the supporting evidence regarding establishment of ARSA activity, and the fact that many patients treated with OTL-200 were close to expected onset of symptoms. However, the ERG is concerned that many patients classified as partial responders by the company do not exhibit this pattern of disease progression, instead remaining stable for a long period (>2 years) followed by decline. The ERG also remains concerned that there is limited evidence to inform the distribution of GMFC states patients will stabilise in, and notes that the revised base-case assumptions do not acknowledge clinical advice elicited from the company's advisory board who considered that around [redacted] of partial responders would stabilise at a GMFC score of 3-4.

The ERG is also unclear on the rationale for the updated assumptions which revise the distribution of GMFC states patients stabilise. While the ERG accepts that the original assumptions were informed by the clinical data, the current assumptions imply that no further progression will occur. This may not be reasonable given the very limited follow in several patients ([redacted] patient had less than 12 months follow up after initial GMFC assessment) and leads to a very different distribution of GMFC states being assumed than was expected by the company's own clinical advisors. The relative absence of data in the PS-EJ cohort also means assumptions are based on the experience of a single patient. Moreover, the ERG considers that plausibility of the modelled distribution is linked to the proportion of partial responders classified as stabilised. As further detailed in Section 4.2.7.1, the ERG has substantive concerns regarding the modelled proportions of stable and unstable partial responders, and considers that more optimistic assumptions regarding the distribution of stable partial responders likely imply that a greater proportion of patients will be classified as unstable partial responders. Given these substantial uncertainties and the difficulties of ascribing the observed declines in GMFC scores to delayed treatment effect or indicative of continuous progression, the ERG considers that the more conservative scenarios presented in the company's original base-case analysis and clarification response represent plausible alternatives to the company's revised base-case assumptions.

4.2.3 Population

4.2.3.1 Modelled population

The primary source of data used to inform the cost-effectiveness model was a *post hoc* subgroup of the integrated analysis, and a retrospective analysis of the Italian natural history cohort (OSR-TIGET). Patients included in the *post hoc* subgroup of the integrated analysis included 24 patients covered by

the marketing authorisation, excluding data from the 3 patients who would not be covered by the marketing authorisation for OTL-200 and a further patient who progressed shortly after treatment, but who would be covered by the marketing authorisation. As previously stated in Section 3.2.1, the ERG does not agree that this final patient should be excluded from the analysis as they would be eligible for treatment. To adjust for this, we present a scenario analysis accounting for this patient in relevant effectiveness inputs. The ERG is otherwise satisfied that the populations in these studies match the NICE scope.

The baseline characteristics of the modelled population include age, sex, GMFC score and level of cognitive function and are summarised in Table 17. Values were informed by data observed in the clinical trial (starting age in PS-EJ and ES-EJ), demographic data on the general population (sex), and clinical opinion/assumption (staring age LI, level of cognitive impairment, and starting GMFC).

Table 17 Baseline patient characteristics

	Starting age	Proportion Male	Proportion with moderate Cognitive impairment	Starting GMFC
Late infantile	18	49.3%	NA	100% in GMFC 0
Pre-symptomatic Early juvenile	45	49.3%	20% BSC/0% OTL-200	100% in GMFC 0
Early symptomatic early juvenile	80	49.3%	20% BSC/0% OTL-200	40% in GMFC 0, 60% in GMFC 1.

The ERG has several concerns about the baseline parameters values applied and their consistency with the OTL-200 trial data.

Firstly, the starting ages applied in the PS-EJ and ES-EJ sub-populations do not match with data reported in Appendix A of the clarification response, where mean age in the PS-EJ population is reported as 42 months and 88 months in the ES-EJ population. These minor discrepancies, however, have little impact on the model results.

Secondly, the mean starting age of 80 months in the ES-EJ cohort represents a significant mismatch with the OSR-TIGET natural history cohort given the starting GMFC scores of 0 and 1. In the OSR-TIGET study EJ patients reach GMFC 4 at an average age of 77 months and GMFC 5 at an average age of 88 months. This significant mismatch is troubling in that it suggests that the ES-EJ population modelled is fundamentally different the patients included in the OSR-TIGET natural history study. It also creates significant problems with regards to the modelling of natural history in the ES-EJ sub-population, as it is impossible to accurately estimate the time spent in GMFC 0 and GMFC 1 for this cohort.

Thirdly, the assumption that a greater proportion of BSC would start the model with moderate cognitive impairment is unjustifiable; baseline characteristics cannot differ by arm without introducing bias into the analysis. This issue is corrected in the ERG scenario analysis.

Fourthly, the modelled distribution of initial GMFC scores in the LI sub-population is inconsistent with the reported initial GMFC scores observed in the integrated efficacy analysis. The ERG, however, recognises that this may be due to the difficulty of assessing GMFC in very young children and considers the assumed values reasonable.

4.2.3.2 Composition of the modelled cohort

Reflecting the marketing authorisation, the OTL-200 the modelled population includes three distinct groups: i) pre-symptomatic late infantile; pre-symptomatic early juvenile; and early symptomatic (GMFC <2) early juvenile. Within the economic analysis, these three populations are modelled separately to allow for the differences in baseline characteristics, natural history and the efficacy of OTL-200 to be reflected. To estimate an incremental cost effectiveness ratio (ICER) for the combined population covered by the marketing authorisation, the ICERs for each group were aggregated as a weighted average based on the expected incidence of patients across the three groups, see Table D2 of the CS. The proportion of patients from each group in the combined MLD model population were derived from a structured expert elicitation process and evidence from epidemiological sources.

Table 18 Quantitative expert elicitation survey results on UK clinical management of MLD (Reproduced from OTL-200 UK Heath Economic Model Advisory Board Report)

Question	Aggregate response (%), Range []
Question 1: What proportion (%) of late infantile (LI) patients would be diagnosed pre-symptomatically	[redacted]
Question 2: What proportion (%) of early juvenile (EJ) patients would be diagnosed pre-symptomatically?	[redacted]
Question 3: What proportion (%) of EJ patients would be diagnosed in the symptomatic phase?	[redacted]
Question 4: What proportion (%) of LI patients would be treated with haematopoietic stem cell transplantation (HSCT) in clinical practice?	[redacted]
Question 5: What proportion (%) of EJ patients would be treated with HSCT in clinical practice?	[redacted]
Question 6: What proportion (%) of patients eligible for treatment with OTL-200 will be LI?	[redacted]
Question 7: What proportion (%) of patients eligible for treatment with OTL-200 will be early symptomatic (ES)-EJ?	[redacted]
Question 8: What proportion (%) of patients eligible for treatment with OTL-200 will be pre-symptomatic (PS)-EJ?	[redacted]

*Proportions applied in the economic analysis

Results of the elicitation process are reported in Table 18. This demonstrates substantial divergence in clinical opinion as observed by the wide range of values elicited. This uncertainty is particularly

apparent with regards Questions 6 to 8 which attempt to directly elicit the proportion of patients in each of the eligible MLD variants. This may reflect the complexity of this question which requires clinicians to integrate opinions on both the proportion of pre-symptomatic patients in each group and the proportion of LI and EJ patients when personal experience may be quite limited due to the rarity of MLD. Further, it is not clear how this approach integrates the use of epidemiological sources which the company claim was used to inform estimates of the proportions used in the economic analysis. The estimated proportions also do not appear to reflect the known epidemiology of MLD which suggests that the LI form of the disease is the most prevalent making up between 40% and 60% of all cases inclusive of late juvenile and adult-onset forms of the disease, this compares with between 20 to 35% for the juvenile (early and late) form of the disease.[12] To explore this uncertainty the ERG presents a scenario analysis which integrates evidence on the distribution of LI and early juvenile patients with the elicited clinical evidence to explore an alternative distribution of patients across the three MLD phenotypes. This analysis is presented in Section 6.

4.2.3.3 Subgroups

Aligning with the three modelled MLD phenotypes, subgroup analysis was presented for the pre-symptomatic LI; pre-symptomatic LJ; and, early symptomatic EJ populations. This subgroup analysis broadly aligns with the subgroup analysis outlined in the NICE scope, which suggested that subgroup analysis considering pre-symptomatic and symptomatic populations should be considered. The ERG considers the exploration of these subgroups to be highly relevant to decision making and that in particular it may be appropriate to consider symptomatic patients separately given the significant differences in the efficacy of OTL-200 in this population and the potential for heterogeneity in cost-effectiveness across these subgroups. Furthermore, the case for applying a 1.5% discount rate is substantially weaker in the symptomatic population as no patients are modelled to be full responders.

4.2.3.4 Diagnostic pathway

While not explicitly stated, the modelled population and incidence of disease used in the budget impact analysis are reflective of current diagnostic patterns, which given the restrictions of the marketing authorisation, is likely to restrict the provision of OTL-200 to the younger siblings of affected children. The availability of an effective treatment for MLD may, however, alter the diagnostic pathway for MLD. Specifically, the availability of effective treatment for MLD may mean it is added to routine new-born genetic testing panels currently used in the NHS. The use of new-born testing would likely have a substantial impact on the profile of treatable patients, resulting in more patients being able to access treatment as well as leading to patients being identified and treated at a younger age than currently modelled. Importantly, this is likely to substantially reduce the proportion of symptomatic patients.

New-born testing may also impact on the efficacy of OTL-200. Clinical opinion reported in the clarification response notes that lack of efficacy of OTL-200 is likely either due the period between treatment and onset of symptoms being insufficient for the drug's effect to become apparent or the presence of underlying disease manifestations prior to initiation of treatment. In this regard, the ERG notes that a retrospective review of baseline characteristics of all pre-symptomatic patients suggested that those patients treated within a few months of predicted symptom onset or who had abnormal neurological findings at screening showed greater evidence of progression. Earlier treatment in these patients may therefore have plausibly improved outcomes for these patients.

When requested to comment on the impact of new-born testing at the clarification stage (Question B22) the company's response noted [redacted] a fact confirmed by the ERG clinical advisor. [redacted]. These timelines suggest that for the foreseeable future the identification of pre-symptomatic patients will only be possible in families with an affected older sibling. The company outlined an expectation that new-born testing would increase the proportion of pre-symptomatic patients treated with OTL-200, and lead to a greater proportion of patients achieving full response. To illustrate the impact of the new-born testing the company presented an additional scenario analysis in which the distribution of patients across the three MLD phenotypes was revised to increase the proportion of pre-symptomatic patients, and assumed that all patients would fully respond to treatment i.e. 100% of patients classified as full responders.

While the ERG recognises that the limitations of the available evidence, the ERG is broadly in agreement with the company that the introduction of new-born screening would positively impact on the effectiveness of OTL-200. As demonstrated in the company's illustrative scenario this is likely to improve the cost-effectiveness of OTL-200, see Section 5.2.4 for results. Whether the introduction of new-born screening would lead to all patients achieving a full response as modelled in the company's scenario is a matter of speculation, but the ERG considers it reasonable to expect that a greater proportion of patients who are currently classified as stabilised partial responders would achieve full response.

4.2.4 Interventions and comparators

4.2.4.1 OTL-200 treatment

The intervention assessed is the ex-vivo autologous lentiviral gene therapy OTL-200. The intervention, as implemented in the model, consists of three stages, each of which comprises distinct

processes: mobilisation and apheresis of the patient's stem cells, myeloablative conditioning, followed by infusion of the transduced cells (the OTL-200 product) into the patient (see Section 4.2.4.1 for further details of the OTL-200 treatment process). Upon completion of the transfusion patients will remain hospitalised at the treating centre for a period of between 4 and 12 weeks until engraftment of the infused cells has occurred.

The minimum recommended dose of OTL-200 is 3×10^6 $CD34^+$ cells/kg (proportion of successfully transduced CD34+ cells varied between 4.2×10^6 $CD34^+$ cells/kg and 25.9×10^6 $CD34^+$ cells/kg in the modelled population). The medicinal product is composed of one or more infusion bags containing a dispersion of 2–10 $x10^6$ cells/mL suspended in a cryopreservative solution. In cases where multiple rounds of mobilisations were required, patients would receive more than one product lot of OTL-200 and these were administrated in succession and considered one dose. As described in Section 3.2.5 the commercial product differs from that evaluated in the integrated efficacy analysis, which is based on a fresh rather than cryopreserved formulation. The cryopreserved formulation has only been used in [redacted] patients, as such, it is currently unclear whether the cryopreserved formulation will achieve the same treatment effects as the fresh formulation. Evidence from some patients receiving the cryopreserved formulation, however, indicates that there may be important differences in ARSA activity suggestive of inferiority to the fresh formula.

4.2.4.2 Current standard of care

The comparator included in the economic evaluation was BSC consisting of established clinical management for MLD. The aim of BSC is to achieve symptomatic relief and provide supportive care for daily needs. The company described BSC as including physical therapy, pain management, management of skeletal deformity, respiratory physiotherapy, anti-convulsant drugs to control seizures, and anti-psychotic medications, as well as enteral nutrition through a feeding tube in cases of dysphagia, and mechanical ventilatory support.

No direct drug acquisition costs were modelled for BSC, with care costs instead applied as part of health state costs. These were applied to patients irrespective of whether patients received OTL-200 or BSC. Health state costs and provision of established clinical management was assumed to increase, with a decline in GMFC score reflecting increasing symptom burden, see Section 4.2.9.2 for further details of costs applied.

In a contradiction of the NICE scope, haematopoietic stem cell transplant (HSCT) was not considered as a comparator in the economic analysis. The company justified this stating that clinical experts advised HSCT is not routinely used in patients with Late Infantile or Early Juvenile MLD and that evidence indicates poor outcomes for HSCT in these patients [13, 14]. The ERG, however, notes that the elicitation exercise reported by the company does in fact suggest HSCT is used in practice,

particularly in EJ patients. Further clinical advice received by the ERG confirmed the use of HSCT in the NHS for the treatment of MLD and suggests that there would be some overlap between the patient group eligible for HSCT and those eligible for OTL-200. In this regard, the ERG's clinical advisor noted that HSCT has shown poor efficacy in patients with evident neuropsychological and/or neurological signs.[15, 16]

Evidence identified by the ERG evaluating the effectiveness of HSCT is limited but does suggest that patients can benefit from treatment, with several studies demonstrating improvements in survival and stabilisation of symptoms over the medium term (<10 years). Limited follow-up means it is currently unclear whether HSCT permanently arrests symptom progression. The current consensus is that HSCT is most likely to be beneficial in patients with less aggressive forms of the disease (juvenile and adult) and suggests that even amongst pre-symptomatic patients, those with the LI form are unlikely to benefit significantly from HSCT. The main reason for this failure is the slow pace of replacement of resident tissue by the transplanted hematopoietic cell progeny as compared with the rapid progression of the disease in these patients.

Implementation of scenarios evaluating HSCT as comparator based on the literature identified by the ERG is likely to be very challenging. Most studies report only limited details of relevant outcomes including symptom progression and survival. Sample sizes are also generally small and much of the evidence is of questionable relevance to current practice given its age and recent improvements in the delivery of HSCT. Given these limitations, the ERG did not attempt to construct alternative analyses in which HSCT was included as a comparator, and considers it unlikely that an appropriate scenario can be developed based on published data. The company's exclusion of HSCT from the economic analysis may therefore be reasonable, but does represent an important omission and is in violation of the NICE scope.

4.2.5 Perspective, time horizon

The company's analysis adopted an NHS perspective only, and did not consider any costs incurred by Personal Social Services (PSS), which is not the perspective preferred in the NICE Methods guide.[17]

A lifetime horizon of 100 years was chosen as it was considered sufficient to capture all relevant differences in costs and benefits between the comparators. The ERG considers the choice of a time horizon reasonable in the context of curative potential of OTL-200. However, the ERG notes that this choice of such a long-time horizon does mean that the comparatively short-term effectiveness evidence is projected over a very long period, increasing uncertainty in the model results. In the context of company's modelling approach, it also means that many input parameters are consider relevant to a paediatric population are extrapolated to an adult population. This issue is discussed further in Sections 4.2.9.2.

4.2.6 Discounting

The base-case economic model presented in the CS used a non-reference case discount rate of 1.5% for both cost and outcomes. The original company submission did not include any significant justification for the use of the non-reference discount rate of 1.5%. The ERG therefore requested at the clarification step for the company to justify this decision. In their response the company noted the criteria outlined in the guide to the methods of technology appraisal, which sets out that "In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved".

The company considered that these criteria were met, highlighting that without treatment patients will experience early death, and noted that the available data suggests that without intervention very early death will occur and that the majority of patients treated with OTL-200 stabilised in health states of GMFC score of 0, 1 and 2 with normal cognitive function, or mild dysfunction. The company further commented that utility values for these health states range from [redacted] to [redacted], and that across a similar period, age and disease matched natural history controls had either progressed to end-stage disease or had died.

The ERG does not agree with the company's contention that the criteria for applying a 1.5 % discount rate are met and considers that the company has failed to fully justify the decision to apply a non-reference discount rate.

4.2.6.1 OTL-200 restores people who would otherwise die or have a very severely impaired life to full or near full health

The ERG agrees with the company that MLD represents a devasting disease that leads to significant impairment and early death. The ERG also acknowledges the potential for OTL-200 to meet the criteria for restoring patients to full or near health insofar as patients fully responding to treatment appear to have retained both cognitive and physical function broadly in line with that of the general population. However, the majority of patients who do not achieve a full response. Under the base-case assumption, this is restricted to 40% of patients in the LI population and 60% of patients in the PS-EJ population. All remaining patients are assumed to either stabilise in the GMFC 1 or 2 states, or exhibit continued albeit slowed progression of disease. Further, the ERG disagrees with the company's assertion that GMFC 1 and GMFC 2 represent near-normal health. As discussed in detail in Section **Error! Reference source not found.**, there are substantive issues with the way in which utility values were derived for the model, including specific concerns that the utilities applied to GMFC 1 and 2 do

not fully reflect the morbidity associated with these health states. The is also broader evidence of cognitive decline in patients treated with OTL-200, it is therefore unclear whether cognitive abilities will be completely retained in patients stabilised in GMFC 1 and 2. The ERG would therefore disagree that a sizable proportion of patients are restored to full or near health as outlined in the methods guide.

With regards to the ES-EJ population, the ERG would also argue that it is difficult to see how these criteria can be met. All patients in this cohort will have definitionally experienced some decline in function representing the fact they are treated with some symptoms of disease. All patients in the ES-EJ population with therefore necessarily not be in full health.

4.2.6.2 Benefits are long-term

As described in Section 5.2.6, the ERG believes there is insufficient evidence to conclude with certainty that benefits of treatment will be truly life-long. Durable clinical efficacy has been demonstrated up to 60 months in a small number of full responders (n=[redacted]); with a maximum follow-up of 77 months, there are no data beyond this. Follow-up for the majority of patients is, however, much shorter (median [redacted] months). There is also uncertainty with regards to surrogate markers of treatment efficacy. For example, issues such as gene silencing and unequal attrition of high VCN cell lines (up to [redacted]) noted in the EPAR could be indicative of future loss of efficacy. The data to substantiate that modelled benefits of OTL-200 are "very likely" to be achieved has therefore not yet been demonstrated.

4.2.6.3 OTL-200 will not commit the NHS to significant irrecoverable costs

The ERG notes that the company response did not refer to the final criteria set out in the methods guide that the introduction of the technology does not commit the NHS to significant irrecoverable costs. The ERG would contend that OTL-200 does not meet this requirement due to the substantial as upfront acquisition costs associated with OTL-200 of ([redacted] inclusive of PAS). These costs would not be recovered by the NHS if the engraftment fails at any point. As outlined in Section 4.2.7.1, there is also limited long-term evidence of graft durability or stability of GMFC scores. Should patients who currently appear stable begin to experience progression of symptoms, then not only would the full cost of OTL-200 have been incurred, but it is likely to result in both significant reductions in the QALY benefits of treatment as well as very substantial increases in care costs. These reductions in benefits and increased care costs may be particularly acute if progression is very slow resulting patients being trapped in health states associate with very low or negative HRQoL and very large ongoing care costs. The ERG appreciates that such a scenario may represent a pessimistic interpretation, but anything less than a complete and indefinite treatment effect amongst stabilised patients is likely to result in both a substantive reduction in the benefits of treatment as well as very substantial increased costs to the NHS.

4.2.7 Treatment effectiveness and extrapolation

4.2.7.1 Effectiveness of OTL-200

Concepts of response and stabilisation on OTL-200

As described in Section 4.2.2.4, the effectiveness of OTL-200 was defined with respect to three response categories: full responders, stabilised partial responders, unstable partial responders. Each category is associated with a specific alternative trajectory expressed in terms of assumed transitions between GMFC health states. The assumptions associated with each trajectory and the proportion of patients assigned to each are central to the calculation of the health benefits and costs associated with OTL-200 and therefore are a main driver of cost-effectiveness.

Full responders were those considered to demonstrate broad stabilisation of motor symptoms and were assumed to have full preservation of motor and cognitive function for the duration of the modelled time horizon. The company considered a 'full response' to treatment to be possible in patients who were truly pre-symptomatic at the time of treatment. This was considered to reflect those patients in the programme of clinical trials whose symptoms did not progress beyond GMFC-MLD 0 over the follow-up period. The company explained that this demonstrated that the treatment effect began prior to onset of the underlying mechanisms of disease, and thus patients could retain essentially full health indefinitely. In full responders, it is assumed that 100% of the treatment benefit is maintained for the duration of the modelled time horizon, with these patients experiencing no onset or progression of MLD symptoms.

The remainder of patients treated with OTL-200 are classed as 'partial responders', which refers in the model to two distinct groups. The first, stabilised partial responders, were described by the company as 'functional stabilisers', as these patients still experience the permanent halt of disease progression after a period of initial decline. The assumption of continued decline followed by stabilisation was based on clinical opinion, and the GMFC trajectories observed in some OTL-200 patients. In the original company base-case all stabilised partial responders were assumed to stabilise in GMFC 2, in spite of clinical advice received by the company which suggested that patients were expected to stabilise across GMFC states 0-4. This assumption was updated in the company's revised base-case so that patients could stabilise in either GMFC 1 or GMFC 2.

A second sub-group of partial responders are not assumed to experience stabilisation and instead have continued progression of symptoms, albeit at a substantially slower rate. The ERG refers to these patients as 'unstable' partial responders. The factor by which disease progression was assumed to slow was derived from comparison between a subset of patients in the OSR-TIGET natural history cohort with patients in the OTL-200 trials, most of whom were excluded from the efficacy analyses

presented in the company submission. Further detail on the calculation of these progression modifiers and the resulting state residence times are discussed in below.

In the company's base-case model, [redacted] of pre-symptomatic LI patients, and [redacted] of pre-symptomatic EJ patients are assumed to be full responders (See Table 19). These proportions were derived from the trial data, based on the proportion of patients remaining in GMFC 0 at their last observation. In the original base-case presented by the company, the split between the two groups of partial responders (stable/unstable) was based on clinical opinion. The company's model was later updated so that the proportion of stable and unstable partial responders was informed by the trial data, though it was not clear how they derived this distinction. These changes resulted in the proportion of stabilised partial responders increasing in the LI and ES-EJ groups and decreasing in the PS-EJ group. In the LI group the proportion of stabilised partial responders increased from [redacted] to [redacted], while in the ES-EJ group the increase was from [redacted] to [redacted]. In the PS-EJ group the proportion decreased from [redacted] to [redacted]. These changes had a significant impact on the results, as the proportion of patients achieving each level of response to treatment is a major driver of modelled treatment benefits, and resulted in the weighted ICER decreasing significantly.

Table 19 Response category proportions in OTL-200 trials (Clarification Response Table B3)

	Full responder N (%)	Partial responder (functional stabiliser) N (%)	Partial responder (slowed progression); N (%)
Pre-symptomatic late infantile (n = [redacted])	[redacted]	[redacted]	[redacted]
Pre-symptomatic early juvenile (n = [redacted])	[redacted]	[redacted]	[redacted]
Early-symptomatic early juvenile (n = [redacted])	[redacted]	[redacted]	[redacted]

Validating the concepts of stabilisation applied in the model using evidence presented presents several challenges. This is primarily due to the model structure necessitating the categorisation and extrapolation of the unique response patterns observed across each of very few patients who have received OTL-200. As discussed in Section 4.2.2.4, the ERG considers the evidence presented to be insufficient to support the existence of the disease trajectories modelled by the company, and to ascertain the likelihood of a patient following a particular trajectory following treatment.

The primary driver of cost-effectiveness in the company's model is the proportion of patients assumed to achieve each level of response. The proportions generated from the clinical data are subject to very high levels of uncertainty, as a number of these response categories are populated by a single patient. Representative model inputs cannot be accurately informed by such limited data, and thus the

frequencies of late-stabilisers and non-stabilisers to be expected if OTL-200 is made available are extremely uncertain.

This is illustrated in the differences between the company's original model in which proportions were based on clinical elicitation, and in the model updated to align with clinical data. The ERG considers both approaches to subject to equally high uncertainty due to the limited duration of follow-up, and very limited numbers in the observed data demonstrating each type of response. The proportions chosen appear internally inconsistent, and do not seem to follow clinical advice to the company. In particular, the ERG questions the assumption that such a small proportion of LI partial responders would experience continued decline compared to PS-EJ, given the aggression of this variant of MLD. According to the clinical rationale explaining each level of response provided by the company, it might be expected that LI patients showing early manifestations of disease at baseline could experience more rapid decline before the OTL-200 treatment effect is established. It is unclear then why [redacted] of patients with the slower progressing EJ variant would be expected to experience continued decline compared to [redacted] in LI, when the natural history of these variants may indicate otherwise.

Proportion of full responders

Even if it accepted that a proportion of patients will experience long-term attenuation of disease symptoms, the classification of which patients are most likely to achieve the full benefits of treatment is highly speculative. The company's approach is based solely on GMFC score and requires the absence of any decline in GMFC at last follow up. The ERG is concerned that this approach is too simplistic and ideally should take a more holistic approach based on long-term stability across all outcome measures. Importantly, the definition does not require a minimum period of follow up. This means that patients can be classified as full responders with despite not having demonstrated stability across multiple follow-ups. This is potentially unreasonable given that there is acknowledged risk of continued progression immediately follow treatment. In the absence of a minimum follow-up requirement, it is highly likely that the proportion of full responders will be overestimated due to the difficulties of distinguishing between slowed progression and true stabilised disease, particularly given multiple examples of patients declining following a long period of apparent stability.

Notwithstanding the inclusion of other measures of disease progression, the ERG considers that a more reasonable definition should include a minimum follow up period informed by the supporting evidence on surrogate disease markers and evidence of late progression in patients with longer follow up.

Establishing an appropriate minimum follow-up period given the limited data available is challenging, as too stringent a requirement will act to further shrink the already very limited data set, while too

short a follow up period increases the likelihood of bias. Examination of evidence on establishment of ARSA activity, which may be useful proxy of the time until replacement of resident tissue, indicates stabilisation of mean ARSA levels in the PMBC reach normal reference levels after just 3 months (Figure C11, CS), but may be as long as 24 months based on data on ARSA levels in the CSF (Figure C12, CS). In both cases there is, however, evidence of substantial variation individual patient experience, and as previously discussed it is not clear how ARSA levels in each system affect impact progression of motor dysfunction.

In terms of GMFC scores, evidence on the time until first drop in GMFC suggests several years of follow up may be required to establish a patient as a full responder. In [redacted] patients classified as partial responders, the initial decline in GMFC did not occur before 24 months. In the absence of longer follow up these patients would have potentially therefore been misclassified as full responders. Stabilisation for 24 months following treatment may therefore be a useful indicator of the likelihood that a patient will continue to respond to treatment and represent a reasonable balance between the desire to maintain the sample size and need to minimise bias. This would also broadly align with the available data on CSF ARSA activity. Section 6 presents an analysis in which patients are only classed as having stabilised if they have resided within a particular GMFC stage for 12 months or longer.

Proportion of stabilised partial responders

The ERG is concerned that the company may have overestimated the proportion of stabilised partial responders. Figure 14 presents examples of patients the company considers to demonstrate a full response (green) and stabilised partial response (purple). Importantly, these patients contribute to the modelled proportions of each response type, however, the ERG considers it very uncertain whether these patients can truly be considered as having stabilised. Figure 14 indicates that several patients classified by the company as stabilised partial responders do not appear to have stabilised. Some patients exhibit a drop in GMFC-MLD level at the most recent follow-up, and others previously declined after a period of apparent stability. This post-treatment GMFC trajectory appears contrary to the model of action proposed by the company. That is, late stabilising patients undergo an initial period of progression before the treatment effect is established, after which point stabilisation will be permanent.

Figure 14 Examples of GMFC-MLD trajectories in patients classified as stabilised (Clarification response Appendix C)

Examples of a pattern of apparent stability followed by a decline in GMFC-MLD stage can be seen in several stabilised partial responders across the three modelled disease variants. This is counter to the pattern of treatment response in partial stabilisers hypothesised by the company, i.e. an initial period of decline followed by a permanent plateau. The ERG considers patients exhibiting the pattern of response described here to be more representative of the 'unstable' group of partial responders, albeit with a slower rate of decline. Scenarios exploring the effect of reclassifying these patients are presented in Section 6.

The case for the existence of late stabilisers in early symptomatic EJ patients appears to be weaker than in the other variants. The ERG considers the evidence available in the EPAR to suggest slow decline across all or almost all participants. A scenario exploring the implications of unstable partial response across more ES-EJ patients (as indicated by the trial data) is presented in Section 6.

Further, the ERG is concerned about the suitability of using the GMFC scores to monitor disease progression in patients treated with OTL-200. While the outcome measures used for modelling purposes (GMFC-MLD state, DQ performance class) are useful for monitoring loss of key motor skills in untreated patients, where disease progression is typically rapid, the broad categories associated with these outcome makes it difficult to differentiate between true symptom stability and slow decline. Each GMFC-MLD state covers a broad range of the Gross Motor Function Measure (GMFM) scale, and is thus insensitive to more gradual change than is observed in the natural course of the disease. It would therefore be plausible for a slow decline in GMFM to be masked by the breadth of the GMFC-MLD staging system, giving the appearance of stability. The existence of slow decline in some apparently stable patients appears to be supported by the GMFM data supplied by the company in their clarification response. In several of the purple-highlighted patients in Figure 14 above, there appeared to be a decline in GMFM total score between years 2 and 3. This suggests that either: a) a number of patients have been misclassified as functional stabilisers; or b) that despite several years of apparent stability of a patient's GMFC-MLD state, disease progression may resume in some patients. Figures presented in the EMA EPAR which have been previously reproduced in Section 3.2.4.3 provide a more granular view of GMFM over time, but different anonymisation systems mean data cannot be matched with those supplied to the ERG by the company. A gradual decline is, however, apparent in several patients, particularly those in the ES-EJ cohort where there appears to be little evidence of functional stabilisers by this measure.

Evidence to support permanent stabilisation

As has been raised in all recent NICE appraisals of one-off treatments with assumed lifelong benefits, a permanent treatment effect cannot be assumed solely on the basis of biological plausibility.[18-21] Whilst medium-term graft stability has been demonstrated in other therapeutics, there are factors unique to all such technologies which may impact the long-term durability of treatment effects. The mode of action in OTL-200 is itself unique amongst available gene therapies, i.e. transduction of haematopoietic stem cells to produce sufficient enzyme levels for cross correction of non-HSC-derivative tissues. As discussed in the EPAR and clinical sections above, unforeseen and poorly understood issues such as gene silencing and unequal attrition of high vector copy number (VCN) cell lines (up to [redacted]) could lead to uncertainties with regards to sustained long-term efficacy. It is therefore important to consider the potential impact of future failure of stabilisation upon decision uncertainty. The ERG presents a number of scenarios illustrating the implications of shorter treatment effect horizons upon cost-effectiveness in Section 6.

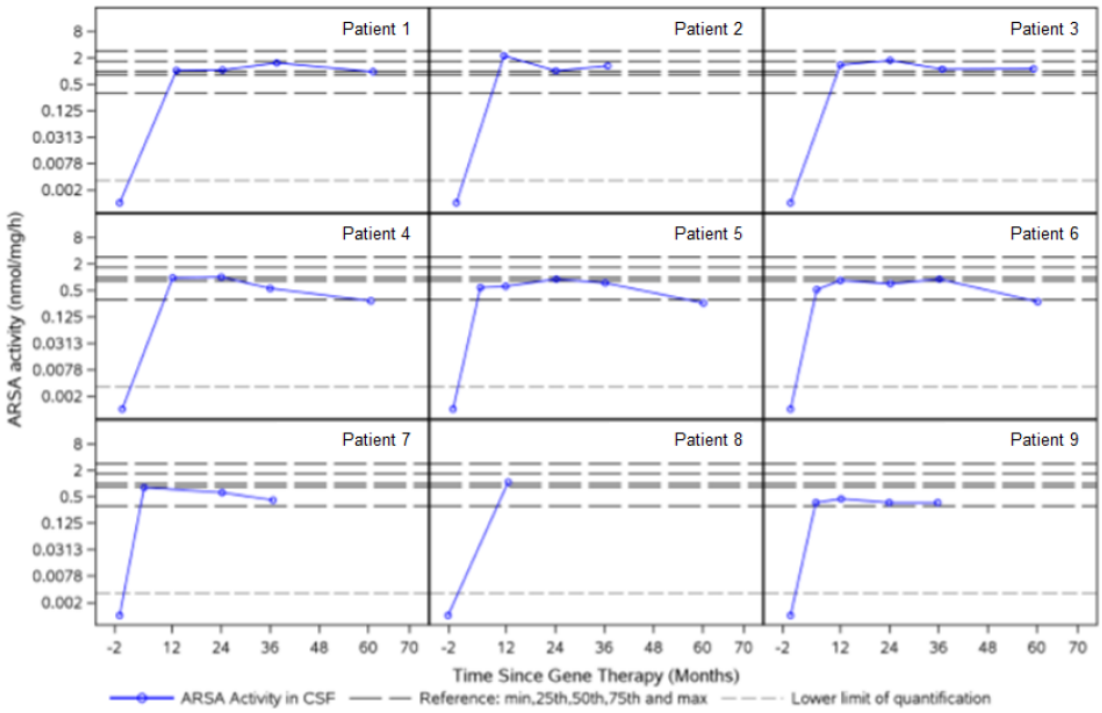
Distinguishing between full arrest of symptom progression and a very slow decline is paramount when considering the long-term implications of treatment with OTL-200. If true stabilisation is indeed observed in some patients, only then can the possibility of a lifelong treatment effect be given

consideration. However, evidence supporting such an assumption must be strong and consistent across domains and outcome measures and should be sustained over a minimum observed period. In order to be classed as a full responder, the company required only that the patient have a GMFC level of 0 at the most recent follow-up. Upon inspection of data provided to the ERG, it appeared that many patients classified as having stabilised (full or partial responders) had little or no follow-up beyond the point of 'stabilisation', and others appear to decline after a period of stability (see Figure #). It is therefore arguable that current data are insufficient to classify patients one way or another.

Further as discussed in Section 3.2.4, there was evidence that OTL-200 does not prevent disease progression across all systems equally. Continued deterioration of peripheral neuropathy in PS and ES-EJ patients treated with OTL-200 was demonstrated by declines in NCV, with no statistically significant difference between treated and untreated EJ patients at Year 3. While small numbers of heterogeneous patients included in these analyses may have led to confounding, these data suggest that OTL-200 may not have as profound an effect upon progressive peripheral demyelination as upon the CNS. While the company state that the relationship between peripheral neuropathy and symptom progression is less well established in the EJ variant, they state elsewhere that it is a major contributor to gross motor dysfunction. It may therefore be plausible that while motor dysfunction driven by CNS progression is halted, progressive peripheral demyelination may lead to eventual progression of motor dysfunction even in full responders.

The levels of ARSA activity generated by engrafted cells may be a useful proxy to understand the potential longevity of the treatment effect. As discussed in Section 3.2.4.8, there are remaining uncertainties concerning the implications of ARSA activity levels over time. However, as highlighted in the European Public Assessment Report for OTL-200, there were declining levels of CSF ARSA activity observed in several late infantile and pre-symptomatic early juvenile patients. The EMA considered it likely that continued efficacy was dependent upon maintaining ARSA activity levels above a certain threshold, however, the company could not determine this threshold upon request. The most recent data available in Figure 15 show CSF ARSA levels to be trending downwards, towards or below the lowest healthy population reference values in most LI patients. This may be cause for caution over the assumption of permanence of the OTL-200 treatment effect in every patient who achieves apparent stabilisation of symptoms. The ERG notes the company's suggestion that [redacted] but notes too that the EMA could not verify this, and that evidence to confirm such a relationship was not provided by the company.

Figure 15 Cerebrospinal fluid ARSA activity over time in LI patients (nmol/mg/h) (Reproduced from EPAR Figure 10)



Note: Values ≤0/undetectable ARSA activity were imputed at LLOQ. LLOQ was 0.0032 nmol/mg/h.
Note: The reference range represents data from a cohort of paediatric reference donors as per Perugia reference report.

Disease progression in unstable partial responders to OTL-200

As previously discussed in Section 4.2.2.4, patients whose symptoms continued to progress during the trial period were designated 'partial responders'. Those who failed to show sufficient evidence of stabilisation were assumed to continue progression until they reached GMFC-MLD 6. The rate of progression applied in the model was based on a comparison of the TIGET natural history cohort with OTL-200 treated patients. This yielded a ratio (progression modifier) to calculate the time patients are modelled to reside in each health state. These patients also experienced much lower rates of moderate to severe cognitive impairment until the later disease stages.

The company calculated these progression modifiers by deriving a ratio which described the relationship between the average time patients took to progress from GMFC-MLD 2 to GMFC-MLD 5 in the TIGET natural history study, with those who experienced an equivalent progression in the OTL-200 integrated dataset. In the TIGET study, patients across both the LI and EJ phenotypes spent an average of [redacted] between entry into GMFC-MLD 2 and reaching GMFC-MLD 5. There were data for only [redacted] patients experiencing this decline. In the OTL-200 clinical trial, the equivalent transition period was [redacted] months (n=[redacted]). The resulting progression modifier derived from the ratio between these two populations was [redacted], which was applied to the state residency times presented in Table 20 to estimate those for unstable partial responders. Time patients with both

disease variants spent in each GMFC state in the natural history study are presented in Table 20 below.

Despite the derived progression modifiers including data on ES-EJ patients, for the purposes of the model the transitions of early symptomatic EJ patients were modelled using a selection of different progression modifiers based on clinical opinion. These progression modifiers can be found in Table 20. Relative to those applied in pre-symptomatic LI and EJ MLD, it was assumed that treated patients remain in the earlier GMFC health states (0 – 3) for longer (ratio [redacted]) but progress through states 3 to 5 more quickly (ratio 2.8), and [redacted] between 5 and 6. There was no adjustment of the time between entering GMFC 6 and death for treated patients.

The progression modifiers applied between the GMFC 0 – 1 and GMFC 1 – 2 health states for ES-EJ were changed from 3.21 to 1.00 in the updated base case submitted by the company at clarification. The company also adjusted the time spent in GMFC 0 – 1 in PS LI and PS-EJ in an attempt to account for the misalignment between the observed and modelled transition times highlighted by the ERG at the clarification stage.

Table 20 Progression modifiers and transition times in company model (adapted from company's executable model)

Transitions	LI BSC (OSR – TIGET) (mths)	PS late infantile		EJ BSC (OSR-TIGET) (mths)	ES early juvenile		PS early juvenile	
		Modifier	Mean time (mths)		Modifier	Mean time (mths)	Modifier	Mean time (mths)
from 0 to 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 1 to 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 2 to 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 3 to 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 4 to 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
from 5 to 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG noted a number of issues with the estimation of the progression modifiers applied to non-stabilising partial responders. Firstly, while the company provided an explanation of the methods used to calculate the progression modifiers for PS LI and PS-EJ patients, it was not clear which patients these calculations were based on. The Company clarification response states that these calculations were based on [redacted] patients treated with OTL-200, but does not further specific the identity of these patients. There are fewer than [redacted] patients classified as unstable partial responders by the company and therefore the ERG considers it likely that this population includes some combination of stable and unstable partial responders. The ERG is also concerned that there may be a greater number of patients in the OTL-200 group with the EJ variant, whilst it appears that most patients with an eligible disease

course in the TIGET cohort had late infantile disease. As the LI variant is more rapidly progressive than EJ, the disease course of the OTL-200 treated patients may have been slower on average than those in the natural history cohort. This may have biased the modelled progression modifiers in favour of OTL-200.

The progression criteria applied to the TIGET data to obtain the base transition values may have also introduced bias. Only [redacted] whose progression time between GMFC 2 to GMFC 5 was recorded were included in this analysis. However, there were data on many more patients available for progression from GMFC 2 to GMFC 6 in the TIGET group, as more rapidly progressive patients did not have a recorded assessment at GMFC 5. This may have resulted in the inclusion of only those patients with a slower disease trajectory, this would have the effect of increasing mean state residence times. Increasing the time patients spend in each state has a different effect upon patients depending upon their treatment group. In general, the longer patients on BSC are assumed to remain alive, the better OTL-200 looks in comparison. This is due to the extremely high resource use associated with later GMFC states, and very strongly negative utilities applied to these patients. Furthermore, as partial responders on OTL-200 are assumed to experience much lower rates of cognitive impairment, they maintain a positive health related quality of life for much longer than BSC patients in equivalent health states. Thus by inflating the time spent in state for all patients, OTL-200 may appear more cost-effective.

Two publications which reported transition times between GMFC 1 and GMFC 6 were identified by the company, and with larger sample sizes appear to show significant discrepancies with the TIGET analysis. At an average of [redacted] months, EJ patients in TIGET appear to spend much longer in GMFC 5 than was observed in Kehrer *et al*. 2011,[22] and Elgun *et al.* 2019.[23] In Kehrer 2011, EJ patients (n=38) spent an average of 12 months in GMFC 5, while this was 7 months in Elgun 2019 (n=32). This was also the case in LI patients, whose GMFC 5 residence time was 2 months in Elgun 2019 (n=29), and 2 months in Kehrer 2011 (n=21), compared to [redacted] months in TIGET. If the use of these figures results in a net increase in the modelled time spent in GMFC 5 and 6, cost-effectiveness estimates may be biased in favour of OTL-200 but may not be reflective of UK clinical practice.

The ERG also highlights the drastically different disease trajectories assumed between EJ patients diagnosed as pre-symptomatic versus those diagnosed with early symptoms. It is unclear why the company considered these groups to be sufficiently different to warrant independent sets of progression modifiers. Whilst both groups are assumed to spend a similar period of time between GMFC 0 and 1, pre-symptomatic patients are assumed to spend over three times longer at GMFC 5 than early symptomatic patients [redacted]. The progression modifier values applied to ES-EJ patients were elicited from the company's clinical advisors. As discussed previously, the ERG

does not consider it appropriate to derive key efficacy inputs from clinical opinion – particularly when the treatment effect has yet to be observed in these patients.

4.2.7.2 Effectiveness of standard care

As described previously, patients in the model's standard of care arm were assumed to receive palliative care which aims to manage disease symptoms but does not impact on the rate of progressive motor and cognitive decline. As such, patients were assumed to experience rapid disease progression in line with natural history. Rates of disease progression were informed primarily from the OSR-TIGET natural history study, with patients age and disease subtype matched to patients from the OTL-200 clinical trials. The OSR-TIGET natural history study was carried out by the San Raffaele Telethon Institute for Gene Therapy (TIGET) in Italy, consisted of a cohort of 31 early-onset MLD patients (19 LI and 12 EJ) managed with best supportive care (BSC) in Italy. Data from the OSR-TIGET natural history was also supplemented by data from Elgun *et al.* (2019)[23] which informed the time to transition between GMFC 0 and GMFC 1 in late infantile patients.

Transition probabilities were estimated for each health state where possible and therefore different risks of progression were estimated for each health state, however, lack of data forced the assumption of a constant rate of progression across heath states GMFC 2 to GMFC 4. Reflecting differences in rates of progression between disease phenotypes with separate transition probabilities estimated LI and EJ patients. Calculation of transition probabilities was based on mean time to transition, with per cycle probabilities estimated assuming a constant hazard. At the clarification step the ERG noted some errors in the calculation transition probabilities these were, however, corrected in updated model. Mean time to transition for each modelled disease variant are presented in Table 21.

Table 21 Modelled 'Mean time to transition' (Based on CS, Table D4 and D5)

Model Transition	Mean time to transition: Late infantile	Mean time to transition: Early Juvenile
GMFC-MLD 0 to 1	[redacted]	[redacted]
GMFC-MLD 1 to 2	[redacted]	[redacted]
GMFC-MLD 2 to 3	[redacted]	[redacted]
GMFC-MLD 3 to 4	[redacted]	[redacted]
GMFC-MLD 4 to 5	[redacted]	[redacted]
GMFC-MLD 5 to 6	[redacted]	[redacted]

The ERG considers the company's approach to the modelling of the transitions for patients receiving standard care to be reasonable, and the data source (OSR-TIGET) was appropriate given the limited data available. As stated in Section 3.2.6, the ERG does have concerns about the matching process that was undertaken to generate the matched cohort, as well general concerns regarding the use of a

non-randomised comparator. This may have implications in terms of the rate of decline predicted by the transition probabilities.

The ERG also has concerns regarding the values used to populate time spent in GMFC 0 and is unclear on how the respective 10- and 28-month periods were derived. Further, the ERG is concerned that the values applied are leading the model to overestimate time spent in this health state and to make predictions that are not consistent with the input data used. This can be illustrated by considering the mean age at which a patient reaches GMFC 1 in the model compared with data observed in the OSR-TIGET study. Using the LI population as an illustrative example, the mean age patients reach GMFC in the model is 28.8 months compared with 21.3 months observed in the OSR-TIGET natural history study. Similar disparities exist in the EJ cohorts. Revision made at the clarification stage to increase consistency between the PS-EJ and ES-EJ sub-populations have further exacerbated this issue and do not address the issue raised in Section 4.2.3.1 of substantial mismatch between the ES-EJ cohort and the natural history cohort. Further, these revisions are inconsistent with evidence from the OSR-TIGET cohort and suggest patients in the PS-EJ cohort only enter GMFC 1 on average after 103 months; in the OSR-TIGET study, EJ patients reach GMFC 5 at an average age of 88 months and GMFC 6 at an average age of 109 months. To explore the implications of these issues the ERG attempts to re-estimate the time spent in GMFC 0 based on data from the OSR-TIGET study and assumed starting age (see Section 6).

4.2.7.3 Mortality

The company's base-case accounted for both disease-related and other-cause mortality. Other-cause mortality was assumed to capture all mortality not directly attributable to progression of the disease and was applied to all health states in the model.

Disease-related mortality was confined to GMFC 6, such that patients had to pass through all other GMFC states before applying any disease related mortality. The company stated that this assumption was informed by evidence from the OSR-TIGET natural history cohort which indicated that no deaths occurred in patients prior to entering GMFC 6. In the original company base-case, per cycle mortality was informed by data on the mean time to death after entering GMFC 6 observed in the OSR-TIGET natural history. This implied a mean time to death of [redacted] months and was used to estimate a per cycle mortality rate by assuming a constant mortality hazard. The [redacted] months in in GMFC 6 months period was applied irrespective of MLD phenotype or treatment received.

Other-cause mortality rates were informed by general population rates adjusted for the age and sex of the cohort, but otherwise unadjusted to account for disability in patients with GMFC >0. Patients in GMFC 0 to 5 therefore were assumed to experience no mortality related to their disease and

consequently, patients classified as functionally stabilised (i.e. full responders and stabilised partial responders) were assumed to have life expectancy in line with the general population.

The ERG highlighted several inconsistencies to the company in the way mortality rates had been applied in the model, which resulted in predictions lacking face validity. These included the observation that general population rates had been misapplied, which resulted in a large proportion of the treated cohort reaching >90 years of age, and the observation that an unreasonable proportion of the untreated cohort was predicted to remain alive well into adulthood. In response to these issues, the company provided a revised base-case that corrected errors in the estimation of transition probabilities and revised assumptions used to model disease-related mortality which were now informed by parametric survival modelling of Kaplan-Meier data from the OSR-TIGET natural history cohort. The company fitted 7 alternative parametric models (Exponential, Weibull, Log-normal, Log-logistic, Generalised Gamma, Gompertz, and Gamma), with the Weibull model selected for use in their base-case analysis, and sensitivity analysis presented to consider alternative models.

Other cause mortality

The company's assumptions regarding other-cause mortality, together with the assumption that patients experience no further disease progression, are among the most important factors in determining total QALYs and costs due to their direct impact on the benefits accrued from halting disease progression. The ERG has significant concerns about the validity of assuming that all 'stabilised' patients will experience general population mortality rates, and considers there to be several reasons to expect that these individuals will experience morality in excess of the general population rates. These arguments relate to three potential risk factors: myeloablative conditioning, continued disease progression, and disease-related mortality not directly attributable to progression of the disease. Each of these is discussed in turn below.

Myeloablative conditioning: The model currently does not account for either the short- or long-term morality risks associated with the myeloablative conditioning regimen that every patient receiving OTL-200 must undergo. Short-term risks associated with myeloablative conditioning include gram-negative sepsis, veno-occlusive disease, and infections which will represent a non-zero excess mortality risk that should be accounted for in the model. Further, the ERG considers that there is the potential for ongoing long-term mortality risks associated with myeloablative conditioning and notes that the clinicians on the OTL-200 HE Advisory board commented that '[redacted]', and that the [redacted], especially in patients expected to survive to around 80 years. In this regard the ERG highlights assumptions accepted in the recent appraisal of betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia, where a SMR of 1.25 was applied to general population estimates of mortality to capture the potential ongoing impact of myeloablative

conditioning. The ERG therefore considers that the company should have made a similar effort to account for the effects of myeloablative conditioning and presents a scenario accounting for this increased risk in Section 6.

Neurological progression: As discussed in Section 4.2.7.1, the ERG considers that the company's interpretation of the clinical data is potentially overly optimistic, and there is significant uncertainty regarding the assumption that stabilised patients experience no further progression of disease. Any relaxation of this assumption will, however, lead to a reduced life expectancy as patients will continue to experience increasing loss of function and as in untreated patients, an early death. As outlined above, the ERG explored alternative assumptions regarding stabilisation in Section 6. These scenarios account for progression-related mortality, using assumptions already made in the company's base-case, i.e. that once patients decline to GMFC 6 their life expectancy will align with patients on BSC.

Other disease-related mortality: While some patients receiving OTL-200 may be expected to retain full or near full function, some partial responders to treatment will only stabilise after a period of decline. Stabilisation following progression of disease will mean that some patients will be stabilised with range of physical and cognitive impairments, including those in GMFC 5 who are bed-bound and unable to sit unaided, and are thus likely to be at increased risk of infection – the primary cause of death in GMFC 6. The impact of this long-term disability may impact on the longevity of these patients, the ERG notes comments made by the OTL-200 HE Advisory board who suggested that '[redacted]'. The ERG therefore requested that the company justify why mortality rates were not adjusted to reflect the nature of the condition and symptoms of patients stabilising in health states associated with significant disability. The company's response emphasised the lack of evidence in MLD to inform these assumptions and noted the expectation that cognitive function would be preserved in patients be in patients who had received OTL-200. The company presented a scenario analysis in which mortality risk (compared to general population) was increased for patients in GMFC 2 - 5 based on scenarios conducted as part of HST12 (cerliponase alfa for the treatment of CLN2).

While the ERG accepts that there is no direct evidence to inform these assumptions, it notes the evidence used to justify the scenario analysis presented in the appraisal of cerliponase alfa. This scenario drew on evidence from people who have suffered traumatic brain injuries (TBIs) and people who had suffered loss of ambulation following a spinal cord injury.[24-26] These studies showed clear evidence that physical and neurological impairment results in increased mortality risks relative to the general population. Moreover, as discussed in Section 4.2.2.2, the ERG disagrees that there is sufficient evidence to support the assumption that OTL-200 preserves cognitive function and highlights evidence that cognitive impairment has a substantial impact on life-expectancy. For example, a UK study using evidence from Clinical Practice Research Datalink database has shown

that cognitive impairment is associated with a near 20-year reduction in life-expectancy compared to adults without intellectual disability. Given this evidence, the ERG considers that mortality rates should have been adjusted in partial responders to reflect the physical and cognitive impairment associated with these health states.

Disease related mortality

The ERG welcomes the company's inclusion of parametric survival models in their updated model, and considers this a superior approach to the original model assumptions, which allows the company to make maximum use of the available survival data. However, the ERG has some concerns about how the company implemented this analysis in the economic model. The first concerns an apparent error in the implementation of parametric survival models, as survival time was measured from birth, rather than from entry into GMFC 6 as per the data source. This does not align with the model structure adopted by the company and leads to the model significantly overestimating survival time. The second issue concerns the choice to implement separate survival models for LI and EJ patients. The ERG is unclear on the motivation for this given that the original base-case assumed a common survival time in GMFC 6. While the ERG recognises the possibility that survival time in GMFC 6 may differ between these two groups, there is little evidence to support this proposition. Nor in the view of the ERG is there a strong clinical rationale for such a difference, as disease-related mortality is primarily driven by infection due to loss of ambulation rather than from pathologies caused directly by the underlying disease mechanism. Survival times in GMFC are therefore likely to be similar in both groups. Combining the data from LI an EJ cohorts also helps to overcome problems of very limited data in EJ patients, where there are only four events. In Section 6 the ERG corrects the highlighted error in implementing the parametric survival models and explores alternative assumptions that combine the survival data from LI and EJ patients.

4.2.8 Health related quality of life

Following the factual error step, the ERG was made aware that the methods used in the TTO exercise as well as some results from the utility study were not described correctly in the CS and company clarification response. This information formed the basis of two important elements of the ERG's critique and led the ERG to question the conduct of the TTO exercise. While the ERG has attempted to revise this section in the light of the new information, the reader should be aware that it was written with these critiques in mind and that the tone a structure reflected deep concerns about the methods of the TTO exercise which are no longer valid.

4.2.8.1 Overview of approach

In the absence of existing data on the HRQoL of patients with MLD, the company commissioned an elicitation study (Nafees 2020,[27] unpublished) to generate health state utilities. Details on the methods

used to generate utilities were provided to the ERG following a further out of process clarification response provided after the factual error report. The following section is therefore based primarily on the ERG's understanding of methodology used following this clarification and does not reflect descriptions provided as part of the formal clarification step.

A total of 24 health states were constructed to represent the experiences of patients with infantile and early juvenile MLD. Infantile MLD health states were defined entirely according to GMFC scores 1 – 6, while for EJ MLD a dimension describing three levels of cognitive impairment was added.

The study relied on vignettes to elicit utilities from members of the general public. These vignettes comprised brief lists of bullet points describing each of the 24 health states used in the economic model. The vignettes describing late infantile MLD were generated through interviews with three specialist consultants in metabolic disorders, while two clinicians and a clinical neuropsychologist with experience assessing cognitive performance in MLD were involved in producing the juvenile MLD descriptions.

Time trade-off interviews were conducted with 100 members of the general public to generate utilities for infantile health states. Another group of 115 participants were recruited to rate the juvenile health states. Half of the participants each rated 9 of the 18 juvenile health states, which were presented to them in a random order. Fourteen of the juvenile MLD scorers rated >7 states inconsistently or 'incorrectly' and were therefore excluded (n=101). Participants were also asked to place each health state (including 'dead') on a visual analogue scale (VAS).

The methods used in the time trade off (TTO) exercise were based on the 'composite TTO' methods as described by Oppe *et al*.[28] Using this method participants were told to imagine they were currently experiencing each health state as described in the vignette, and were presented with standard TTO choices: A) to live in the health state for a period of 10 years followed by death; B) to live for X years in full health followed by death, or c) to indicate that the two previous options were equally desirable. The time (X) spent in full health in choice B) was changed using the 'ping-pong approach', in which the participant was sequentially offered options from either end of the scale of 0 to 10 years, until they were indifferent between the choice between life A and life B. In cases when the number of years in Life A was zero (meaning immediate death) and the participant still preferred Life A to Life B, participants were asked considered a health state worse than death and were moved on to complete the lead-time version of the TTO valuation procedure. Under the lead-time procedure participants were asked a similar sequence of questions, starting with whether they would rather live 10 years in full health then die, or live 10 years in full health followed by 10 years in the particular MLD health state outlined in the vignette. The implication of a resulting utility of -1 is that participants would

rather die immediately than live 10 years in full health followed by 10 years in a particular health state.

Mean time trade off values for the late infantile health states were not adjusted prior to implementation in the model (see Table 22). However, presumably due to the apparent inconsistencies in mean TTO values generated by participants for early juvenile health states, the company used a linear regression model to predict EJ utilities on the basis of GMFC and cognitive function. These modelled values were used in the economic model. The mean TTO values are compared with those generated from the regression model in Figure 16, which illustrates the high level of uncertainty associated with many of the more challenging health states, while some were rated as better than others which the company considered 'worse' in their regression model. It is also notable that utility predicted by the regression model for GMFC 6 + severe cognitive impairment (SCI) was substantially lower than the mean TTO value.

Figure 16 Comparison of mean TTO values with company's regression model for EJ MLD (adapted from Nafees *et al*. 2020)

The utilities generated from the regression analysis for EJ patients as applied in the company's executable model are presented in Table 22. There was no explicit treatment effect on the utilities applied, but as discussed in Section 4.2.2.2, the motor and cognitive components of MLD were disconnected in treated patients. This means that treated patients were generally assumed to follow a much less severe trajectory with respect to their HRQoL as they progressed through GMFC stages 0 to 4.

Moderate cognitive impairment in EJ patients is associated with a disutility of between [redacted] in GMFC 0, increasing to [redacted] by GMFC 6. The disutility associated with severe cognitive impairment is between [redacted] over these states.

Table 22 Health state utilities applied in the company's economic model (Reproduced from CS, Table C28)

Health state	Late infantile	EJ (normal cognition)	EJ (moderate cognitive impact)	EJ (severe cognitive impact)
GMFC 0	-	-	[redacted]	[redacted]
GMFC 1	[redacted]	[redacted]	[redacted]	[redacted]
GMFC 2	[redacted]	[redacted]	[redacted]	[redacted]
GMFC 3	[redacted]	[redacted]	[redacted]	[redacted]
GMFC 4	[redacted]	[redacted]	[redacted]	[redacted]
GMFC 5	[redacted]	[redacted]	[redacted]	[redacted]
GMFC 6	[redacted]	[redacted]	[redacted]	[redacted]

A separate set of utilities was applied to patients with late infantile MLD in order to capture the differential effects of impairment of motor skills on younger children, and the reduced impact of cognitive impairment upon their perceived quality of life. In the company's original model, EJ utilities were then applied to LI patients upon reaching their fourth birthday. The ERG highlighted that this led to unrealistic jumps in the utilities applied to particularly those in GMFC states 2 and 3, who jumped from [redacted], and [redacted] respectively. In the company's updated analysis, they chose to apply the LI utilities to these patients for the duration of the model. That is, utilities based on infants were applied to patients treated with OTL-200 for the entirety of their adult lives.

The utilities of caregivers and patients in GMFC 0 with normal cognitive function were adjusted as patients aged according to UK population norms using a formula based on work by Ara and Brazier.[29] However, the company assumed HRQoL peaks at birth, and began applying age-related utility decrements from age 1 onwards. Furthermore, as utilities for other health states were not adjusted, patients who stabilised in GMFC 1 had a higher utility than those in GMFC 0 after a number of years.

4.2.8.2 Use of Non-reference case methods

The utilities applied in the model are unfit for decision making purposes, and are inconsistent with the NICE reference case. The value set captures only public preferences and includes no explicit consideration of the quality of life of patients themselves. The company appear to have misunderstood the reference case brief, arguing in their clarification response that directly generating public preference weights using TTO is the standard method for eliciting utilities under NICE methods guidance. In adopting this method, the company have not only failed to acknowledge the lived experience of patients and caregivers, but have applied a value set in which many states lie significantly outside the range of established UK EQ-5D preference weights.

The NICE reference case stipulates that quality of life data should be reported directly from patients using EQ-5D, and when this is not possible, it should be obtained via a proxy with experience of the condition, e.g. from caregivers in preference to healthcare professionals. The EQ-5D tool is widely validated in many patient populations, and preference weights have been carefully constructed for the UK population through high-quality research. If the company considered the EQ-5D to be inappropriate for this appraisal, the reference case states that evidence must be provided that shows the tool performs poorly in construct validity tests and responsiveness in this population. Qualitative empirical evidence on the lack of content validity must be provided, demonstrating that key dimensions of health are missing. No such evidence was presented by the company to justify the methods used in the present appraisal, nor could they validate the utilities generated. The intention of NICE cost-utility analyses is not to directly model public preferences, but rather to represent the patient's own perceived quality of life through the lens of public preferences via a validated tool such as EQ-5D. This also reflects the desire of decision-makers to measure health effects across appraisals on the same scale. It is beyond the remit of the company to generate public preference weights for the reasons precisely due to the issues highlighted over the following sections, i.e. without sufficient methodological rigour and participant numbers, such efforts will fail to produce realistic utilities meeting NICE's requirements.

Notwithstanding the small sample size and conduct of the company's utility elicitation exercise, in bypassing patients and caregivers entirely the cost-effectiveness analysis as currently presented cannot claim to represent their perspective. Likewise, the study cannot claim to represent the preferences of the general public. As discussed below, the very poor between-participant agreement across almost all described health states means the company cannot claim these values to demonstrated public consensus on their respective values.

The approach taken by the company in HST12 (Cerliponase alfa for late infantile neuronal ceroid lipofuscinosis (CLN2))[30] may have been a satisfactory compromise, in which eight clinical experts completed the EQ-5D-5L as a proxy for patients in each described health state, although eliciting utilities from caregivers using a validated tool would have been preferential.

4.2.8.3 Methods and results of the utility study

Content of the vignettes

The ERG noted a number of flaws in the methods used to elicit utilities in the TTO exercise described by the company. These flaws manifested in internally inconsistent results which appeared to correspond poorly to external data sources.

The first issue in the conduct of the study regards the content and construction of the vignettes. The ERG questions more generally whether even well-designed vignettes can plausibly equip healthy

adults to comprehend the life of a child with MLD. However, the vignettes make little attempt to provide context for the symptoms they describe. For example, the vignettes describing late infantile health states do not mention that they are imagining the life of a young child who is likely to still be early in their development of mobility and communication. The specific losses in capabilities seen between the descriptions of late infantile GMFC 2 and GMFC 3, for example, are likely to be perceived very differently from the perspective of a healthy adult, i.e. those participating in the study, to that of a pre-school child. Participants ascribed a utility of [redacted] to a health state in which 'you wobble a lot when you walk and move, are unsteady and fall', but a worse than death utility of [redacted] when this level of walking was lost in GMFC 3. Whilst a healthy adult may view confinement to a wheelchair as representing a loss of independence and ability to perform daily living skills, it is unclear whether a regression to crawling would have the same impact upon a pre-schooler's perception of their life.

The descriptions of equivalent GMFC stages appear to be inconsistent between the LI and EJ variants. Trouble with sight and vision loss occurs 'sometimes' according to the vignette describing infantile GMFC 2, and permanence is implied in GMFC 3. However, in the vignettes describing the early juvenile health states, there is no mention of sight and hearing loss. While GMFC 2 in LI was assigned a utility of [redacted], the equivalent health state in EJ was considered only slightly worse than full health ([redacted]), however, it is unclear whether this would remain the case if sight and hearing loss were included in the EJ vignette. As the company have presented no evidence to suggest that sight and hearing are preserved in patients treated with OTL-200 who progress to GMFC 2, it is likely that this utility overestimates the quality of life of treated patients in these health states, especially in patients with preserved cognition who likely place a greater value upon these abilities. The ERG requested that these discrepancies be resolved, as they led to implausible jumps in HRQoL when LI patients turned four. In response, the company applied LI utilities to these patients for the duration of the model. This is clearly inappropriate, and the ERG considers that in theory, the utilities generated for EJ patients would be more representative of older patients with MLD.

While the company stated that the vignettes were reviewed by clinical experts, it remains unclear this feedback was represented in good faith in the descriptions. For example, the advisory panel neuropsychologist described how while children with MCI felt frustrated at not being able to do the things they want to do, progression to SCI is characterised by a loss of interest and loss of responsiveness. The neuropsychologist also reported that 'it is difficult to determine whether children with severe cognitive impairment feel frustration'. However, every vignette describing health states including SCI described children as feeling 'very frustrated when you are unable to do things you want to do'. This, along with the omission of sight and hearing loss described above may indicate that

the vignettes provided to participants may not be a complete or accurate description of the health states.

There is more general evidence that participants had difficulty distinguishing between the health states. For example, participants assigned a higher mean TTO utility to GMFC 2 + SCI [redacted] than to GMFC 1 + SCI [redacted], and GMFC 6 + SCI was rated better [redacted] than GMFC 5 + SCI [redacted]. Unfortunately, comparisons with VAS could not be made due to numerous reporting errors in the utility study. Further inconsistencies are discussed below, and indicate that patients did not fully understand the study, or the health states they were being asked to imagine. While the company's regression model attempted to correct for such discrepancies, they are indicative of underlying issues with the conduct of the study.

Time trade off methods used

The ERG considers the time horizon of the TTO task to be potential source of bias. For states worse than death, participants are to imagine being in the health state for 10 years after a period of 10 years in full health. The experiment may have thereby artificially worsened the perceived utility associated with a health state. It is understandable that participants are likely to have a stronger aversion to committing to 10 years in a particularly negative health state than only one year. Participants would therefore be willing to trade off proportionally more time in full health to avoid the 10 years spent in a worse than death health state. Given the rapid course of disease progression in MLD, no health state would be experienced for such a long period in reality, thus the responses may be biased as a result. A simple re-framing of standard TTO tasks over shorter periods may have served to reduced bias.

The results of the TTO exercise also unsual patterns of response with responses tending towards the best and worst possible ratings. This is highlighted in Figure 17 which shows significant clustering of results around -1, 0, and 1 occurred across the range of health states. The most common response to the TTO exercise was -1, i.e. participants would rather sacrifice 20 years of life, half of which was with MLD and the other half in full health, than ever experience symptoms of MLD. The scarcity of responses distributed between -1 and 0 indicated that those patients who ranked a health state as worse than death sought to avoid it at all costs, with negative TTO responses almost universally rated at -1. The fact that 12% of participants' responses were too inconsistent to be included in the analysis set further supports the contention that participants understandably failed to grasp what is a conceptually demanding and abstract questions put to them.

Figure 17 Histogram of all TTO scores across all health states (Nafees *et al. 2020)*

Agreement between participants appears to worsen when cognitive impairment was added into health state descriptions of early juvenile MLD. As seen in Figure 18, it appeared that for most of the health state descriptions involving severe cognitive impairment, responses were spread across the entire range of possible utilities. There was some evidence of bimodality in these responses – those who completed the LT-TTO task, were most likely to choose -1 in every instance, while positive utilities elicited through conventional TTO were spread more evenly. Across most SCI health states, there were still many participants responding that they would not trade off any life in full health to avoid MLD symptoms, with only GMFC 5 & 6 producing zero responses with a utility of 1.

It is difficult to establish why such a pattern of response may emerge. On explanation is that the participants who moved to the LT-TTO task were those that struggled to grasp the TTO exercise and that these results simply reflect this lack of understanding. It may be, however, be that these results are a true reflection of the public's perception of the impact of MLD related disability and in particular the impact of the loss of cognitive function which was observed to have a very significant impact upon utilities. As discussed below, it is unclear to what degree that these preferences reflect patients lived experience with a risk that they instead reflect societal values and misplaced public understanding of the impact of disability.

Figure 18 Histograms for TTO scores across GMFC 0-6 with severe cognitive impairment (Nafees *et al* 2020)

Inconsistency between TTO and VAS ranking methods

Participants' ratings of each health state on the VAS showed a number of inconsistencies with the results of the TTO component of the study, further suggesting that participants did not fully understand the study, or the health states they were being asked to imagine. Participants ranked health states on a scale between 0 and 100, with 0 being the worst health state imaginable. Participants were also asked to rate death on this scale, with scores rescaled to place death at 0. Unfortunately due to numerous reporting errors in the utility study highlighted by the company, comparison between VAS scores was not possible.

While eight of the 18 juvenile health states were assigned worse than death utilities through the TTO method, the same patients ranked only three health states as being worse than death on the VAS scale. These health states were GMFC 6 + MCI rated at [redacted]; GMFC 5 + SCI rated [redacted]; and GMFC 6 + SCI rated [redacted].

Due to the conceptual simplicity of the VAS method and the lower relative standard deviations around each mean VAS value, these scores are likely to be a better indicator of the participants' perceptions of the health states as described to them. This further demonstrates that participants were likely to

have misunderstood the health states and the TTO exercise itself, or were not equipped to do so by the vignettes provided.

Summary

The ERG has concerns with respect to the study methodology used in the TTO exercise and the face validity of the resulting values, with evidence of unusual distributions of responses. These issues in the non-reference case elicitation study mean that these data are not fit for purpose, and do not represent the lives of children with MLD. While the ERG suggests alternative approaches, the scenarios presented are illustrative in nature, and explore the implications of alternative assumptions upon estimates of cost-effectiveness and thus decision uncertainty. The ERG recommends that the company reconsider the methods used to elicit utilities, and to undertake an exercise in line with NICE methods guidance, and with other appraisals of similar conditions (e.g. HST12).

4.2.8.4 Face validity of generated values

The ERG very strongly contests the validity of the utilities as currently implemented in the company's model, which imply extreme suffering in patients with late-stage disease and limited cognitive function. Indeed, the lives of patients on BSC in the company's base-case model generate [redacted] QALYs, implying that the net negatives of living with MLD outweigh any benefits of having lived at all. If MLD patients indeed experienced such uniquely unremitting suffering, this would be expected to be better reflected in the testimony of clinicians and caregivers around the quality of life of these children.

The ERG's main concerns regarding the face validity of the elicited utilities are twofold: The very severe effect of cognitive impairment upon utility estimates reflects only public perceptions of cognitive impairment, and not how a patient with cognitive impairment feels themselves. This leads to patterns of HRQoL decline that lack face validity when compared with established clinical understanding of the interaction between cognitive and physical aspects of health.[32-35] The ERG also takes issue more generally with use of such strongly negative utilities, which fall well below the lowest utility ascribed to the worst health state as valued by the UK general public, and are likely to represent by far the lowest utility applied in a NICE appraisal. While the ERG appreciates the particular difficulties associated with living with MLD, comparison with health states in other disease areas suggests a lack of external validity.

There is a large and independent effect of cognitive impairment upon the modelled utilities for EJ MLD, which persists in magnitude as patients experience loss of motor function. This is perhaps to be expected, given that the vignettes comprised a largely objective description of symptoms, rather than explaining each health state through the lens of a patient's level of awareness of, and capacity to have feelings about their situation. This means the utilities essentially scale linearly with increasing

cognitive impairment as motor dysfunction progresses. It may have been the case that despite some attempt to describe the patient's feelings about their condition in the vignettes, the company's regression analysis eliminated any such nuance in the modelled utilities, instead applying a flat disutility for each tier of cognitive impairment.

Participants, however, showed clear bias against health states involving cognitive impairment. For example, a substantial proportion of participants would rather die immediately than ever experience cognitive impairment, even after a long period of full health. The very significant effect of cognitive impairment alone upon utilities with no motor symptoms of MLD (mean TTO utility decrement of [redacted]) is concerning, and suggests the exercise is biased by social attitudes towards a loss of cognitive capacity, reflecting the participants' feelings towards a loss of their own personhood, rather than imagining themselves in the life of a child with cognitive impairment.

The ERG questions the validity of the position that a child with very limited cognitive function would have a worse perception of their own quality of life than a child who was fully aware of their condition in later health states. Indeed, this is supported in the vignettes provided to participants – in which patients with severe cognitive impairment at GMFC 6 are described to have limited awareness of their environment and to be asleep most of the time. In contrast, those with preserved cognitive function at GMFC 4 are described to feel irritated and angry that they are unable to do what they want to do, often feeling sad and upset, and to worry a lot about their condition. The ERG's clinical advisor agreed with this interpretation, and suggested that in the natural course of MLD, the crossover between discomfort and pain with some preserved cognitive awareness results in the greatest distress experienced by patients in GMFC 4 and GMFC 5, before tailing off as patients become more unresponsive and spend much of their lives asleep in GMFC 6.

The assumption of an additive relationship between motor dysfunction and cognitive capacity is not supported by evidence across a wide range of conditions, and was not considered plausible by the ERG's clinical advisor. It has been established in numerous studies that in conditions associated with cognitive impairment such as dementia in adults,[33] the primary channel through which reduced cognition affects HRQoL (as measured by EQ-5D) is through its influence on daily living functionality, i.e. the lost capacity to perform tasks necessary to live and care for oneself independently.[33-35] It may therefore be the case that the patient's perception of their own quality of life would not be affected additively by both the loss of communication, skills, and independence due to gross motor dysfunction, and then again by cognitive impairment. Evidence in children with sickle cell disease demonstrated a clear relationship between cognitive abilities and the effect of disease severity on HRQoL. Hardy *et al.* found that higher IQ was correlated with a higher HRQoL in patients with mild disease, but in those with moderate to severe disease all patients had an equally poor HRQoL, which demonstrated no correlation with cognitive function.[32] However, there is evidence to

suggest that EQ-5D alone may not adequately capture the effects of cognitive impairment upon HRQoL.

The ERG therefore argues that patients who are already entirely dependent upon others to perform daily living tasks will experience little or no additional impact upon their perceived HRQoL with increasing cognitive dysfunction. A disutility should therefore be applied only in health states where patients would otherwise be able to care for themselves. This is particularly the case in patients at GMFC 5 and 6 who are bed-bound and incapable of any movement or communication. It could indeed be argued that patients with preserved cognition would experience a substantially worse quality of life than those who are unresponsive and unconscious almost all of the time with pharmacological management of pain and other symptoms. Experts involved in the company's advisory board stated that being cognitively aware of poor physical health is a consideration in the patient's perception of its severity. The utility of these patients may be more readily compared to death as opposed to very significantly worse than death. In other areas, patients with severe cognitive impairment and complete loss of motor function are considered for modelling purposes as having a 'near-death' quality of life, with a utility of 0.08 – 0.11 for those in a 'persistent vegetative state' (though the ERG acknowledges that these utilities were bounded at zero).[36, 37]

In their clarification response, the company provided a number of examples of conditions in which they believed cognitive impairment was demonstrated to have an independent effect upon EQ-5D, including Prader-Willi syndrome, Fragile X syndrome, and dementia. They also cited a study which concluded that utilities elicited through a caregiver proxy resulted were substantially lower in patients with severe cognitive impairment than those elicited directly from patients themselves.[38] The ERG considered none of the studies provided by the company to demonstrate an independent relationship between cognitive impairment and HRQoL, as each of the cited conditions is confounded by physical disability or demonstrable bias from caregivers. The relationship between cognitive impairment affects HRQoL in dementia has been previously discussed.

The ERG's second primary issue with the applied values concerns the extent and magnitude of negative utilities. To the ERG's knowledge, the utility representing GMFC 6 + SCI is by far the most negative utility applied in a NICE appraisal, and is applied throughout the majority of the lives of BSC patients. The magnitude of this utility was partially a product of the company's regression analysis, with the predicted value at the lowest end of the confidence intervals for the mean TTO responses for this health state.

The face validity of these particularly negative values is questionable when compared with the UK EQ-5D-3L/5L value set, in which the lowest possible value is -0.594. This represents UK general population's perceived value of the worst health state described by the EQ-5D tool, and is the scale

upon which HRQoL is valued in NICE appraisals. The ERG further notes that the UK EQ-5D-3L value set is unique in the use of such negative utilities,[39] with all other countries having higher minimum values and far fewer health states described as worse than death. Furthermore, other generic measures with UK value sets such as the SF-6D includes no worse than death health states.[40] The introduction of a health state with a utility of [redacted] therefore appears to imply suffering beyond the established worst health state as imagined by a very large sample of the general public, and is inconsistent with general commentary around the UK public's preferences. The ERG suggested that the company reconsider the widespread use of strongly negative utilities in their clarification questions. Unfortunately the company's response did not address the ERG's concerns with regards to the magnitude of the negative utilities applied. Instead, the company provided examples of other diseases in which worse than death utilities have been implemented. However, the worst utility among these was for patients with the most severe level of multiple sclerosis (Expanded Disability Status Scale (EDSS) 9), which was associated with a utility of -0.195.[41]

The company summarised the results of a survey of MLD caregivers (n=20), in which caregivers reported the impact of MLD on their child's quality of life. These data do not appear to support the company's position that the lives of children with MLD are not worth living. The sample appeared to mainly comprise caregivers of patients with more advanced disease, as 95% of patients were reported as being unable to walk. While the company reported insufficient data to map the PedsQL Score onto EQ-5D, a mean total score of 32.7 (out of 100, population norm 77.8) indicates that caregivers do not consider their children to have a life worse than death, with an average psychosocial score of 47.1 indicating that they consider a life with MLD worth living. The PedsQL data are arguably methodologically superior as an indicator of patient preferences to the value set elicited from the general public, and at the least demonstrate a preference for life among patients and caregivers living with MLD.

To explore the impact of the cognitive utility decrements, the ERG presents several alternative scenarios in which the cognitive decrements are fully or partially removed in Section 6.

4.2.8.5 Age adjustment

There are two errors in the company's interpretation and application of age adjustments in the model. Firstly, utilities were only adjusted as patients aged in GMFC 0, and only in patients with normal cognition/mild impairment. Once patients with moderate cognitive impairment reached the age of 76 their utilities drew level with patients with normal cognitive function, and were tied to the normal value from then on.

This means that patients who stabilised in GMFC 1 had a higher utility than those who stabilised in GMFC 0 from approximately age 36 onwards, and at around 56 onwards for those stabilising in

GMFC 2. There is no reason to assume that the HRQoL of these patients will not decline in line with the rest of the population. Secondly, the Ara and Brazier predictive equation has been inappropriately used to extrapolate the relationship between HRQoL and increasing age outside of the sample upon which it was based. The data used to derive this relationship comprised members of the general population aged between 16 and 98. The basis of this relationship is the increasing burden of co-morbidities people experience as they age. The approach taken by the company assumes that HRQoL peaks at birth (using a utility derived from adults), and deteriorates from patients' first birthday. These issues are both addressed in scenario analysis presented in Section 6.

4.2.8.6 Caregiver quality of life

Caregiver disutilities arising from the physical and mental health burden associated with caregiver activities were captured by administering the EQ-5D-5L to 21 caregivers, 6 of whom lived in the UK (Pang *et al*., 2020).[9] Anxiety and depression were most commonly reported (71% [15/21]), with moderate to severe pain/discomfort experienced by 62% of respondents. EQ-5D-5L values were cross-walked to UK population weights reported in Szende *et al*., 2014.[42] Based on the responses of all 21 participants, a disutility of -0.108 was applied to caregivers. The company assumed that there would be zero caregivers required until patients reached GMFC Stage 5, at which point two caregivers were required, both of whom incurred the caregiver disutility of -0.108 (total -0.216).

This input appears to be derived from the company's Advisory Board Report, in which clinicians reported that professional social care was required from GMFC 5. This may have been an error, as the submission is clear that UK caregivers (i.e. parents and family) spend the vast majority of their time caring for their child with MLD (average 15 hours per day).

The ERG is concerned that the company appear to have misinterpreted clinical opinion over the necessity and extent of parental care throughout the earlier stages of MLD. The company's application of caregiver disutilities only for patients in GMFC Stages 5 and 6 appears to be inappropriate. Clinical advice received by the ERG indicated that the significant limitations and needs of patients at GMFC 3 and GMFC 4 would require considerable and constant supervision and intervention from caregivers. The ERG was also informed that in virtually all cases, full time care and supervision would be necessary from at least one parent once patients reach GMFC 2 and beyond. The physical burden of feeding and managing children in the earlier stages of the condition mean that it would be more appropriate to apply the full caregiver disutility from GMFC 2 onwards. The effects of this assumption are explored in Section 6.

4.2.9 Resources and costs

The company's model included OTL-200 acquisition costs, administration costs, along with health state costs associated with the management of MLD. The acquisition and administration costs of

OTL-200 include pre-administration work-up costs and post-transplant hospitalisation and monitoring costs. Health state costs attempted to cover all aspects of care for children with MLD and included medical costs, supportive medications, healthcare equipment and social services costs.

Unit costs were sourced from a number of national sources, including NHS Reference Costs, the British National Formulary, the electronic Marketing Information Tool (eMIT), and the Personal Social Services Research Unit (PSSRU).[43] The key costs included in the model are summarised in Table D22 to D24 of the CS, and a detailed description is provided in Section 12.3 of the CS. The perspective taken by the company's economic analysis is that of the NHS and PSS, in line with the NICE reference case.[44] However, the company noted that there may be considerable costs associated with the management of the disease that fall outside of this perspective that are not captured in this analysis, and suggest that the use of OTL-200 may be associated with even greater costs savings than suggested by the cost-effectiveness analysis. These include out of pocket costs that are borne by families and carers, such as for adaptive beds, saliva suction machines, and for adapting vehicles. The company note that any funding available for these adaptations is rarely sufficient to cover the full costs to the family.

4.2.9.1 Cost of OTL-200

The total cost associated with the technology per treatment/patient (including the administration costs) for OTL-200 was estimated by the company to be [redacted] based on the OTL-200 list price, and [redacted] with the OTL-200 PAS price. The total cost per patient includes the price of the technology, leukapheresis (cell harvest), pre-transplant conditioning, administration, and follow-up costs for two years after transplant. The costs are summarised in Table 23.

The costs of treating adverse events associated with OTL-200 were assumed to be covered by the administration and follow-up costs, and were not accounted for in the model. The company considered them to be mostly mild or moderate, or occur within a short time following treatment.

Table 23 Summary of costs associated with administration and treatment with OTL-200 (adapted from Table D25 of CS)

Items	Value	Source
Price of the technology per treatment/patient	[redacted] [redacted]	List price for OTL-200. *PAS price for OTL-200.
Leukapheresis (cell harvest)	£4,272	Weighted average of HRGs for stem cell (SA34Z) and bone marrow harvest (SA18Z). National Reference costs – 2018/19
Conditioning	£7,899	HRG for paediatric metabolic disorders hospitalisation non-elective inpatients (weighted average cost = £7,761) Busulfan costs = £138 per patient [eMIT].[45] Busulfan 60mg vial – 8 pack = £367.81). Average dose of Busulfan in trials = 176mg
Administration and hospitalisation	£24,188	HRG paediatric metabolic disorders admissions weighted average elective inpatient (weighted average cost = £5,068). However, the SMPC states patient would stay about 4 – 12 weeks (average of 7.5 weeks) in the hospital, which is about 6 weeks longer than that reported for metabolic disorders inpatient admissions in Hospital Episode Statistics of 11 days (E75.2). The weighted average cost of elective inpatient excess bed day HRGs was calculated to be £460.73 (i.e. £5,068 /11). Thus, overall hospital stay is calculated as £24,188 (i.e. £5,068 + [41.5 x 460.73])
Follow-up transplant costs	£61,965	Hettle *et al.* 2017.[46] Follow-up costs for allogeneic stem cell transplants. Discharge to 6 months = £28,390, 6–12 months = £19,502, 12–24 months = £14,073.
Total cost per treatment/patient	[redacted] [redacted]	Calculation, based on list price *with OTL-200 PAS price

The ERG considers that the costs described for the administration of OTL-200 are generally lacking in detail and omit some small but important aspects of the treatment pathway, such as clinical laboratory and monitoring tests throughout the pathway, and prophylaxis of seizures and VOD during conditioning. These costs are relatively small and would form a small proportion of the total associated costs and so are not explored further. Some specific points regarding the estimation of OTL-200 administration costs are described below.

Cost of screening patients

The company's model does not incorporate the cost of initial baseline assessments in patients who are screened for eligibility for treatment with OTL-200. As per the SmPC, eligibility for treatment with OTL-200 should initially be assessed by the treating physician via a full neurological examination, motor function assessment, and neurocognitive assessment, as appropriate for the patients' age.

Costs incurred by patients screened but who do not receive OTL-200

The company only estimates and applies the cost of treatment with OTL-200 for those patients who are screened at baseline and successfully infused with OTL-200. However, as acknowledged in the SmPC, prior to the commencement of conditioning, "the treating physician should ensure that autologous HSPC gene therapy administration remains clinically appropriate for the patient, and that treatment with [OTL-200] is still indicated".

The ERG noted that not all patients screened would be deemed eligible for treatment with OTL-200 (page 119 to 120 of the CS). There were at least four patients screened but found not to be eligible for treatment. Therefore, there may be some patients who do not receive treatment with OTL-200 but have associated resources whose costs are not accounted for. These include those who initiate baseline screening but are found not to be eligible for treatment, or who experience failure of mobilisation.

Moreover, it is not clear whether the NHS would have to incur the cost of OTL-200 for those patients who were deemed eligible for OTL-200 treatment at screening but who deteriorated and became ineligible for treatment after the time that the product was produced at OSR-TIGET. In such cases, the NHS would bear the substantial cost of treatment but receive none of the associated treatment benefits. The risk of this occurring is not negligible: at the clarification stage, the company provided evidence for one patient ([redacted]) who was excluded from the Integrated Data Set, who [redacted]. This is equivalent to just under [redacted]: the true risk will emerge with the treatment of more patients, and is likely to differ between patient subgroups. Clarification from the company on whether the NHS would bear the cost of unrequired product is essential.

Missing AE costs

The ERG does not agree that the majority of AEs associated with OTL-200 were mostly mild or moderate, since 69% of trial patients had a serious AE, see Section 3.3.1. In the regenerative medicines HTA, an assumption was made that all grade 3 and 4 adverse events require an extension of hospitalisation by 1 day, with a cost based on the excess bed-day HRG cost.[46]

Inappropriate transplant costs and post-transplant costs

The company estimated the cost of administering OTL-200 using the HRG for paediatric metabolic disorders admissions, adjusted to the mean duration of hospital stay as stated in the SmPC. The ERG

considers that the cost associated with an alternative HRG code (Peripheral Blood Stem Cell Transplant, Autologous, Code SA26B) is more appropriate. This cost, at £34,539 per episode, is marginally higher than the cost estimated by the company, at £24,188 per episode.

The cost of monitoring and treating patients for two years after treatment with OTL-200 was obtained from an HTA on regenerative medicine,[46] which used the cost reported in an NHS Blood and Transplant analysis (2014).[47] These costs are considered to be of limited relevance to the present decision problem, as they were originally from a costing study of patients with acute myeloid leukaemia and acute lymphoblastic leukaemia receiving an unrelated adult donor transplant, and was conducted in the Netherlands between 1994 and 1999.[48] These likely overestimate the post-transplant costs after OTL-200.

4.2.9.2 Health state costs

The company did not identify any relevant resource use studies for the NHS in England. Therefore, to inform resource use in the economic analysis, the company conducted a study to estimate health care resource use (HCRU) associated with the management of MLD, eliciting expert opinion from five (six people recruited to the study, but one person declined to provide answers) clinical experts. The clinical experts were from the three lysosomal storage disorders reference centres in the UK, in which metachromatic leukodystrophy (MLD) patients are managed, and included paediatric haematologists, consultants in paediatric inherited metabolic diseases, and clinical neuropsychologists.

Clinical experts involved in the study were asked to provide information on the frequency, duration and proportion of HCRU for MLD patients in the UK, including a wide variety of medical visits and equipment use, with social caregiver usage, in each GMFC-MLD stage. Data from an Italian clinician with direct experience of treating patients with OTL-200 provided the basis for the types of resources considered, and where no response was given, these values were carried forward. The results of the study were then aggregated, and the mean usage of each resource were calculated for use in the model.

Resource use by GMFC-MLD health state, estimated by the HCRU study, are presented in

Table 24. Some unit costs and resource use in health states GMFC-MLD 4 to 6 vary by age group (child or adult), but are very similar. The company assumed that patients in GMFC-MLD 0 would not require any medical resources related to management of MLD, beyond an annual hospital visit. The same health state costs were applied in both the OTL-200 and the BSC arms of the model.

Table 24 Summary of monthly MLD-related medical costs for MLD from UK HCRU study (ages 0-5)

Cost category	GMFC-MLD health state							
	State 0	State 1	State 2	State 3	State 4	State 5	State 6 (at home, 80%)	State 6 (in hospital, 20%)
Drugs	£0	£198	£229	£235	£235	£254	£263	£263
Medical tests	£0	£156	£74	£74	£74	£76	£74	£74
Medical visits and procedures	£0	£311	£307	£634	£680	£547	£558	£558
Hospitalisation	£49	£78	£233	£350	£551	£641	£1,011	£14,248
Emergency	£0	£9	£13	£15	£20	£23	£27	£27
Healthcare equipment	£0	£34	£40	£76	£76	£91	£91	£91
Respite care	£0	£0	£0	£0	£0	£0	£0	£0
Social services	£0	£0	£0	£0	£0	£0	£2,550	£9,120
Total	£49	£785	£897	£1,385	£1,636	£1,632	£4,573	£24,380

There was little variation in drug usage across the GMFC-MLD stages in both percentage usage and mean days used per year, indicating the pharmacological management of MLD is consistent throughout progression, with the notable exceptions of amoxicillin, Oramorph, and scopolamine patches. The drugs that accounted for the greatest proportion of monthly drug costs were the antiepileptics phenobarbital, levetiracetam and clonazepam. The mean number of medical tests per year was largely consistent across health states, except in the case of GMFC-MLD 1 where it was mostly higher, potentially reflecting an opinion that such tests would be used in the initial diagnosis. The number of medical visits were also largely consistent across states, indicating an all-or-nothing engagement with a given service. A single expert indicated that half of GMFC-MLD 4 patients may require salivary gland Botox.

There was a small increase in frequency and duration of inpatient hospitalisation between health states GMFC-MLD 1 to GMFC-MLD 6 (home). Patients who were assumed to be almost fully hospitalised in GMFC-MLD 6 (hospital) were assumed to spend 292.2 days in hospital. The unit cost of hospitalisation was estimated from NHS Reference Costs, using a weighted average of Paediatric Metabolic Disorders (HRG code PK72A, PK72B, PK72C). Costs were estimated as an average of non-elective inpatient HRGs (£7,761 per episode) and elective inpatient HRGs (£5,068 per episode), and the mean cost per day per episode was estimated by assuming that the duration of each episode was 11 days. The mean number of patients requiring emergency admittance for an MLD-related acute event also increased with GMFC state, although comprising a small proportion of total costs.

MLD patients were also considered to require the near-universal provision of a pram/stroller, walker, and ankle/foot orthosis. A car for transporting wheelchairs (the cost of which assumed to be included in the wheelchair service and not included in the model), an adaptable bed with anti-decubitus mattress, and a pulse oximeter/aspirator/cough machine were required beyond GMFC-MLD 3. The study also indicated that a normal highchair (required for all health states), bathtub aids and an enteral feeding pump are also required resources for patients with MLD, but costs of these were not included in the analysis as they were not reported by NHS Reference Costs.

In the original company model, social service usage was not considered to be required until patients reached GMFC 4 and included costs to account for the costs of enteral nutrition support and other care needs. This assumed that in GMFC-MLD 4 to 6 all patients would require a social worker to provide enteral nutrition support for 8 hours of the day on 292 days of the year. On top of this, further social care costs were included to account for other care needs, applied in GMFC 5 and GMFC 6, including in patients who were assumed to be permanently hospitalised. Following concerns raised at the clarification stage regarding the face validity of these costs, the company removed all costs associated with enteral nutrition; however, social care costs were retained in GMFC 6. For patients treated primarily at home this was modelled as 85 days per year of social care, assuming 7.2 hours provision per day. For hospitalised patients this was modelled as 304 days per year of social care again assuming 7.2 hours provision per day. Costs for a social caregiver in both cases were obtained from PSSRU, and assumed costs of £50 per hour for children and £51 for adult services.

The ERG accepts that there is there is little published evidence available on the resource use of patients with MLD, and the necessity of basing resource use on clinical expert opinion. The ERG, however, has some concerns about that the reporting of the HCRU study. Specifically, the company did not provide clinicians' individual answers to the HCRU questions and it is therefore unclear to what degree there is consensus on resource requirements, and which values were defaulted to the Italian perspective.

Moreover, the ERG has several specific key issues with resource use estimates utilised. These related to: i) the costs associated with OTL-200 full-responders, ii) the costs associated with end stage disease, and iii) the fact that the analysis does not sufficiently differentiate between the resources used to care for adult patients and paediatric patients.

Costs in health state GMFC-MLD 0

The cost-effectiveness analysis in the company's original submission did not include any MLD-related resource use costs for patients in GMFC-MLD 0. This was questioned by the ERG at the clarification stage. While these patients would be restored to general population health, the ERG does not consider it reasonable to assume that there would be no monitoring of patients previously

diagnosed with a life-threatening condition and treated with myeloablative conditioning and gene therapy. For example, the SmPC states that the patient should be monitored for any signs of leukaemia or lymphoma during the routine yearly check-ups, and monitoring for anti-ARSA antibodies (AAA) is recommended for up to 15 years post-treatment.

The company considered that monitoring costs for OTL-200 patients in GMFC-MLD 0 are assumed to be captured in the follow-up transplant costs accrued in all OTL-200 treated patients in the 2 years post-treatment. Nevertheless, the company updated the base-case model to include all patients (including those in GMFC-MLD 0) having at least one annual visit a year as monitoring for 18 years after treatment with OTL-200.

The ERG considers that there are other costs associated with supporting patients who experience a "full response" to treatment. Clinical advice received by the ERG suggested that symptoms relating to the PNS may have an inferior response to the mode of action of immune stem cell transplants, and there will be some patients classified as full responders who may continue to develop some symptoms relating to peripheral neuropathy. This may result in neuropathic pain in the fingers and legs, controllable with painkillers such as gabapentin and or pregabalin. Full responders may also experience paraesthesia, resulting in a loss of fine motor skills. Patients are likely to require some kind of walking aid even for short distances and may prefer to use a wheelchair over long distances.

Care in the end stages of the condition

The ERG considered that the predicted costs accrued by patients in the end stages of disease and particularly GMFC 6 are very high and potentially lack face validity when compared with values applied in other HST appraisals of metabolic conditions e.g. CLN2. The ERG is specifically concerned that the heath state costs overestimate the frequency and costs of hospital/hospice stays associated with living in GMFC 6, as well as the social care costs applied across health states GMFC 4 to 6.

Costs accrued in the GMFC 6 health state are a modelled on the basis that 80% of patients are cared for in their home, with the remaining 20% of patients are cared for in hospital or a hospice full time. However, clinical advice received by the ERG suggested that patients in the end stage of disease spend the majority of time at home with full time care from a parent. Patients require hospitalisation for resolving specific acute medical needs, such as to manage a status epilepticus, gastrostomy fitting, or to treat a serious infection. It is unlikely that patients would require extended periods of time hospital care except in the most exceptional circumstances e.g. such as when patients experience a very extreme deterioration in symptoms and the family has been unable arrange the necessary adaptations for the home. In this regard, the ERG notes that model already accounts for hospitalisation costs for patients cared for at home, and that these costs are likely to better reflect these incidences of

hospitalisation. The ERG therefore explores scenarios in Section 6 where it is assumed that all care will occur in an at home setting.

Further, the ERG notes that the costs applied to reflect long-term hospice and hospital stays were based on reference costs for inpatient stay in hospital (paediatric metabolic disorders). The ERG considers that this approach is likely to significantly overestimate the care costs because they represent an acute care setting rather than a chronic long-term setting. This approach also represents the costs of hospital stay not a hospice, which the clinical advisor to the ERG suggested would be the main stay of any long-term provision. These concerns regarding the costs of hospice/hospital care were raised with the company at the clarification step. In their response the company presented a scenario analysis with re-estimated daily hospice and hospital costs to account for the patients would not be treated in an acute setting. The ERG considers that this cost is more appropriate, though notes it still assumes 50% of patients are treated long-term in hospital.

The ERG is also concerned that the revised assumptions do not reflect the model of care that is likely to be provided by the NHS and social services. Advice received from the ERG's clinical advisor suggested that care would predominantly be provided in the home and that social care support would not be routinely provide to patients on a regular basis except in certain circumstances, such as within a single parent household, or if there was change in care needs that required constant supervision (e.g. overnight supervision of respiratory needs). The social care costs modelled in GMFC 5 and 6 may therefore not be justified. The ERG, however, recognises that there will be variation in provision and notes comments from carers elicited by the company that suggests families will have access to paid caregivers funded by the local councils. The inclusions of some social care costs as modelled in the revised base-case may therefore be reasonable, though the magnitude of these costs is difficult to quantify. The ERG does not agree that it is appropriate to add additional social care costs for patients who are cared for in a hospital or hospice setting, and considers that any care needs will be covered by the hospital/hospice costs already applied. The ERG therefore considers that these costs should be removed and explores scenarios reflecting this in Section 6.

Costs in OTL-200 adult health states

The model predicts that there are a significant proportion of patients who receive OTL-200 and have a partial response, meaning that disease progression is slowed or halted, and that these patients would survive into adulthood. The company analysis assumes that resource use in adult patients is largely the same as those for children in the equivalent health state. While this may be the case for many resources, such as medication, monitoring, medical visits and hospitalisation, the costs of social care may increase significantly as patients enter adulthood and parents become less able to rely on family members for their care needs.

Consultation with the ERG's clinical advisor suggested that it is likely that an adult in health states GMFC 2 or worse will require some degree of care from social services, and that from GMFC 3 onwards, it would not be possible for patients to live independently and would require either significant in-home assistance or institutional/residential care. In response to concerns raised by the ERG regarding the appropriateness of the health state costs for an adult population, the company applied revised health state costs from 18 years of age. These revised costs assumed that once MLD patients progressed to GMFC 3 (loss of ambulation), a proportion of would be managed at long term care facilities, quoting the NICE appraisal of cerliponase for CLN2 as the source of these rates.[30] The cost of a local authority own-provision care home for adults requiring physical support is £989 per resident week, provided by PSSRU. However, the ERG noted that these costs are outdated, and that the social services and hospitalisation requirements in the more severe health states were not adjusted for inflation (i.e. daily hospitalisation or support for enteral nutrition). The ERG explores a more plausible scenario for adult care, presented in Section 6.

5 COST EFFECTIVENESS RESULTS

The cost effectiveness results outlined in this section are provided from a corrected and updated company analysis following the ERG's clarification questions and subsequent model corrections. All of the results presented in the following sections include the simple PAS discount for OTL-200.

The company made the following changes to the base-case analysis presented in their original submission:

- Update of the probability formula to estimate transitions between health states;
- Mortality in the GMFC-MLD 6 health state (parametric extrapolation of survival data from LI and EJ natural history, based on age at death/censoring);
- Progression modifier for PS LI and PS-EJ removed from movement between GMFC 0 to 1 and from GMFC 1 to 2, assumed to provide disease progression equivalent to natural history to account for pre-engraftment progression;
- Progression modifier for PS LI and PS-EJ modified based on updated calculations to better reflect the relationship between the OTL-200 and natural history cohorts;
- Distribution of ES-EJ patients across GMFC 0 and GMFC 1 health states, updated to align with the OTL-200 clinical trial data;
- Clinical trial data to track proportion of patients stabilising in GMFC 2
- Addition of a monitoring cost in GMFC-MLD 0.

5.1 Company's cost effectiveness results

Table 25 presents the deterministic results of the company's base-case analysis of OTL-200 versus BSC. The results are reflective of the combined cohort of LI, PS-EJ and ES-EJ patients, with the distribution of patients in each subpopulation informed by clinical opinion (Section 4.2.3.2).

OTL-200 was associated with increased costs (cost difference of [redacted]) and was more effective (gain of [redacted] QALYs), compared with BSC. The company's base-case ICER was [redacted] per QALY.

In the OTL-200 arm, acquisition costs of OTL-200 accounted for [redacted] of total costs. Of the medical costs associated with management of MLD, [redacted] of these were accrued by patients in GMFC 2, and [redacted] by patients in GMFC 6 despite only [redacted] of life years generated in this health state (reflecting the high associated monthly costs). While medical costs accrued in GMFC 0 accounted for only [redacted] of total medical management costs, a large proportion of life years ([redacted] of the total life years) and the greatest proportion of QALYs ([redacted] of the total QALYs) were generated by patients in this health state.

In the BSC arm, the costs of hospitalisation and of social care accounted for the greatest proportion of costs, at 40.8% and 42.5% respectively. Of the medical costs associated with management of MLD, the vast majority of these (92.4%) were accrued by patients in GMFC 6. The majority of life years gained were also accrued in GMFC 6 ([redacted]).

Table 25 Results of the company base-case analysis (combined MLD cohort)

Technology	Total lifetime			Incremental lifetime			ICER (£/QALY)
	Discounted costs	LYs	Discounted QALYs	Discounted costs	LYs	Discounted QALYs	
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and QALYs discounted at 1.5%, presented LYs are undiscounted							

A subgroup analysis of each of the eligible MLD disease cohorts were undertaken (Table 26). The ICERs for OTL-200 compared with BSC ranged from [redacted] to [redacted] per QALY gained, with OTL-200 being more cost-effective in the early juvenile pre-symptomatic subgroup.

Table 26 Results of the company base-case analysis (MLD subgroups)

Technology	Total lifetime			Incremental lifetime			ICER (£/QALY)
	Discounted costs	LYs	Discounted QALYs	Discounted costs	LYs	Discounted QALYs	
Late Infantile (Pre-Symptomatic)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early Juvenile (Pre-Symptomatic)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early Juvenile (Symptomatic)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and QALYs discounted at 1.5%, presented LYs are undiscounted							

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) by running 1,000 iterations of the economic model. In each iteration, the model drew inputs from defined distributions for selected parameters.

Combined MLD cohort

The mean probabilistic ICER of OTL-200 in the combined MLD cohort of LI, PS-EJ and ES-EJ patients was [redacted] per QALY gained versus BSC.

The deterministic and probabilistic mean ICERs were very similar (a difference of [redacted] per QALY); however, the confidence intervals around the mean cost and QALYs and the cost-effectiveness plane showing there was not insignificant variation in the probabilistic results (Figure 19), with incremental QALYs varying from [redacted] to [redacted].

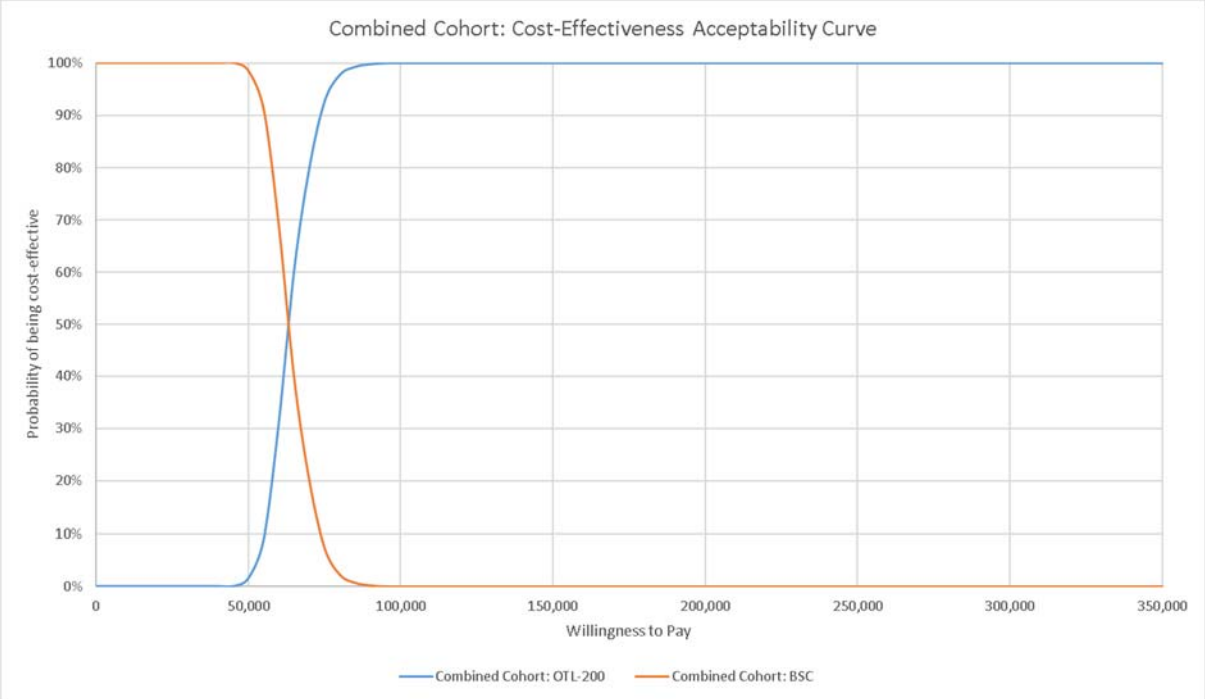
Table 27 Mean probabilistic results of the company base-case analysis (combined MLD cohort)

Technology	Total lifetime [95% CI]			Incremental lifetime			ICER [95% CI]
	Discounted costs	LYs	Discounted QALYs	Discounted costs	LYs	Discounted QALYs	
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and QALYs discounted at 1.5%, presented LYs are undiscounted							

Figure 19 Cost-effectiveness plane of the company's probabilistic analysis (combined MLD cohort)

The cost-effectiveness acceptability curves for OTL-200 and BSC in the MLD combined cohort is provided in Figure 20. The probability that OTL-200 is the most cost-effective treatment option at WTP threshold of £50,000 is [redacted], and at a threshold of £100,000 the probability increases to [redacted].

Figure 20 Cost-effectiveness acceptability curve for the company's analysis (MLD combined cohort)



MLD subgroups

The mean probabilistic results of OTL-200 compared with BSC in each MLD subgroup are presented in Table 28. As with the results of the combined MLD cohort, the mean probabilistic ICERs for OTL-200 compared with BSC were very similar to the deterministic ICERs, and ranged from [redacted] to [redacted] per QALY, with OTL-200 being more cost-effective in the early juvenile pre-symptomatic subgroup.

Table 28 Mean probabilistic results of the company base-case analysis (MLD subgroups)

Technology	Total lifetime			Incremental lifetime			ICER (£/QALY)
	Discounted costs	LYs	Discounted QALYs	Discounted costs	LYs	Discounted QALYs	
Late Infantile (Pre-Symptomatic)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early Juvenile (Pre-Symptomatic)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early Juvenile (Symptomatic)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The cost-effectiveness acceptability curves for OTL-200 and BSC in each of the MLD subgroups are provided in Figure 21 to Figure 23. In the PS LI group, the probability that OTL-200 is the most cost-effective treatment option at WTP threshold of £50,000 is [redacted], and at a threshold of £100,000 the probability increases to [redacted]. For the PS-EJ subgroup, the respective probabilities are [redacted] and [redacted], and in the ES-EJ subgroup the respective probabilities are [redacted] and [redacted] for thresholds of £50,000 per QALY and £100,000 per QALY.

Figure 21 Cost-effectiveness acceptability curve for the company's analysis (late infantile pre-symptomatic group)

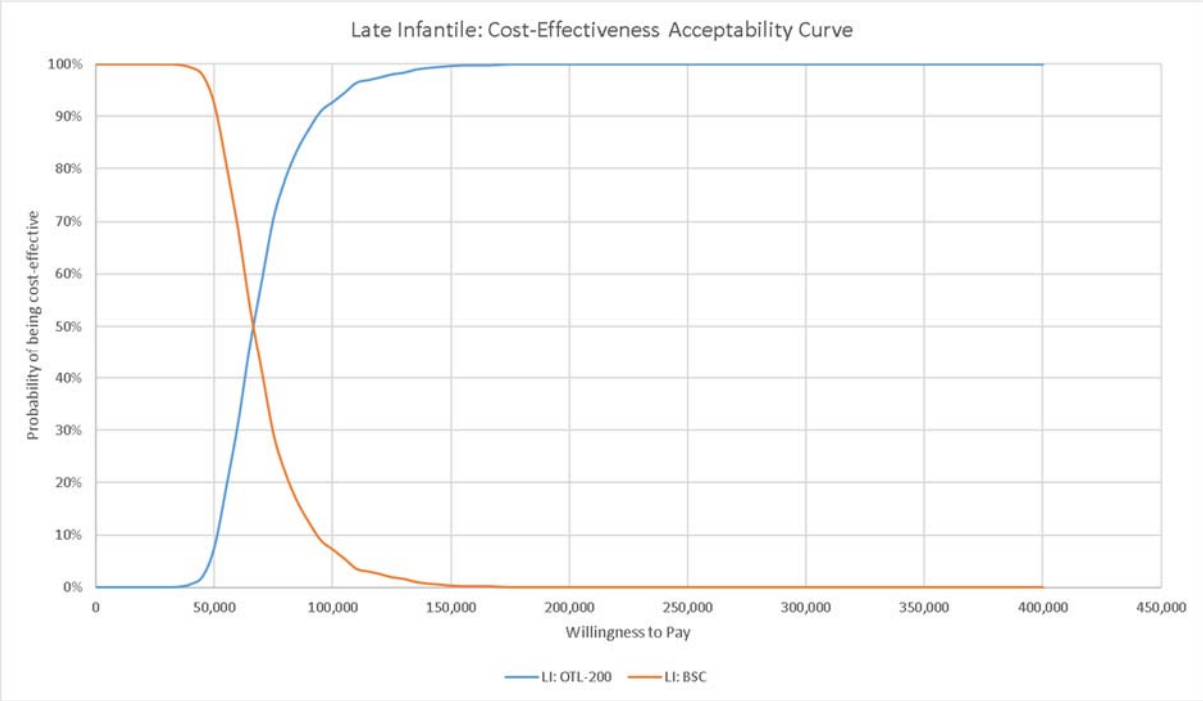


Figure 22 Cost-effectiveness acceptability curve for the company's analysis (early juvenile pre-symptomatic group)

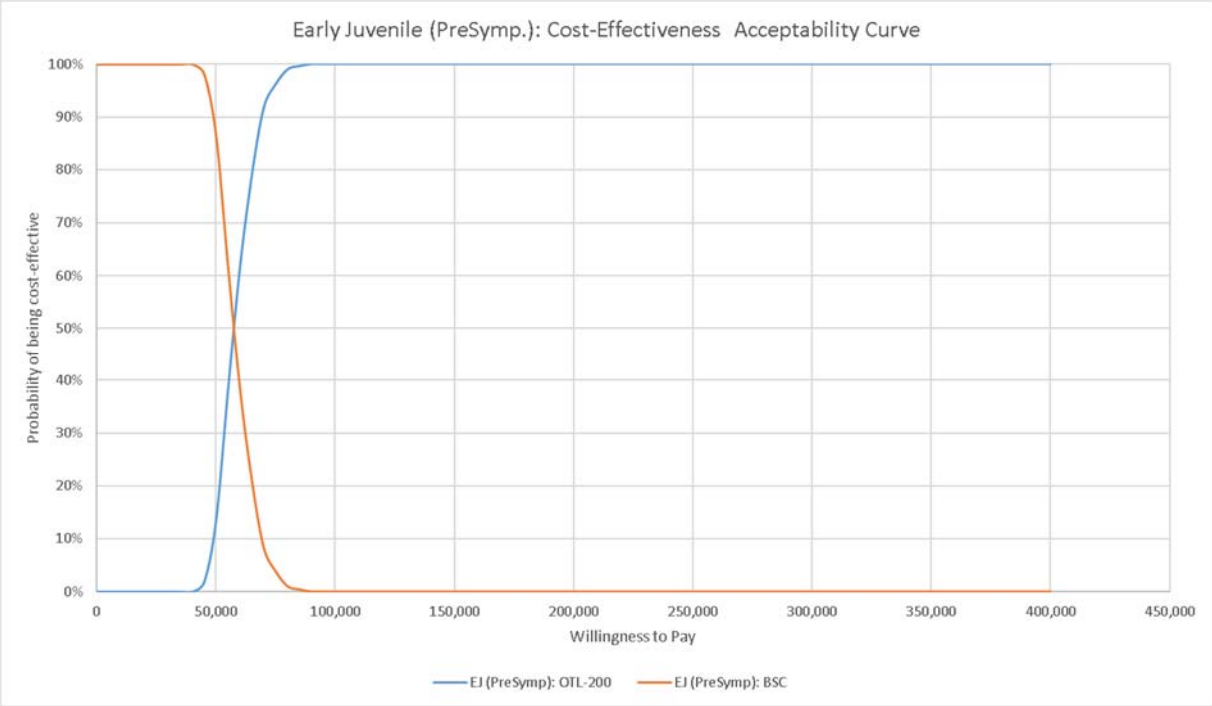
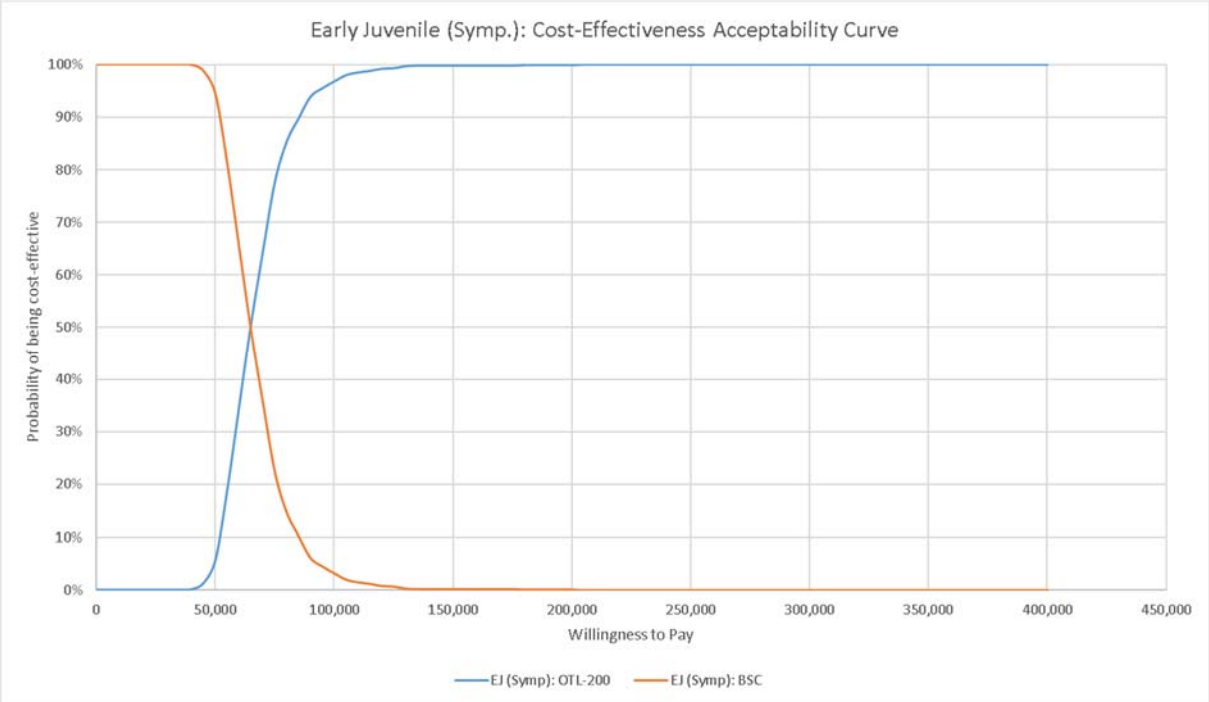


Figure 23 Cost-effectiveness acceptability curve for the company's analysis (early juvenile symptomatic group)



5.2.2 Deterministic sensitivity analysis

The company presented a series of deterministic sensitivity analyses (DSA) in the form of univariate sensitivity analyses to assess the impact of varying key model input parameters upon the ICER. All parameters were varied by ± 20%, or within natural limits of the value (i.e. probabilities varied between 0 and 1) if varying parameters by ± 20% fell outside of these natural limits.

A tornado diagram summarising the 20 influential parameters as reported by the company is presented in Figure 24, which was produced by the ERG from the updated model provided by the company after the clarification stage.

The results indicate that the proportion of stabilising partial responders in the ES-EJ population has the greatest impact on the ICER when varied by ± 20%. In the base case, the proportion of stabilising partial responders in the ES-EJ population is [redacted]: reducing the proportion to [redacted] results in an [redacted] increase the ICER, and increasing the proportion to [redacted] results in an [redacted] decrease to the ICER. The only other variables that impacted on the ICER by [redacted] or greater in either direction was the proportion of responders in the PS-EJ population and the proportion of responders in the PS LI population.

It should be noted that the method by which the company developed the DSA. i.e. varying each parameter by ± 20%, does not explore the uncertainty associated with each parameter as it does not account for the specific uncertainty associated with each parameter. A better approach would have been to use the limits of the confidential interval for each parameter. Thus while the univariate sensitivity analyses show that there is little variation in the ICER, suggesting that the results of the cost-effectiveness analysis may be robust to a wide range of assumptions, this may not be the case if there is uncertainty associated any particular parameter is more appropriately explored.

Figure 24 Results of the company's univariate sensitivity analysis for OTL-200 vs BSC (combined MLD cohort)

5.2.3 Scenario analysis

In addition to the univariate scenario analyses presented in Section 5.2.2, the company also presented results of scenario analyses on a number of other parameter values. The results for the combined MLD population are presented in

Table 29.

Most notably, using the 3.5% discount rate for costs and benefit increases the ICER to £[redacted] vs BSC. The rate of response to OTL-200 was also an influential parameter in the analysis: when the proportion of full responders are increased, the ICER vs BSC decreased by [redacted]. The use of more conservative percentages of full responders increased the ICER by [redacted].

Applying alternative, increased number of caregivers for the caregiver disutility and time to engraftment had a minimal impact on the ICER, and the use of alternative natural history sources, progression modifier values gathered from the SEE, and proportion of ES-EJ patients in the combined MLD population had a modest impact on the ICER.

Table 29 Results of the company's scenario analyses for OTL-200 vs BSC (combined MLD cohort)

Scenario	Base case value	Lower limit	Upper limit	ICER at lower limit	ICER at upper limit
Discount rate					
Discount rate for costs and benefits	1.5%	0%	3.5%	[redacted]	[redacted]
Caregiver disutility					
Number of caregivers required for caregiver disutility	GMFC-MLD 2: 0 GMFC-MLD 3: 0 GMFC-MLD 4: 0 GMFC-MLD 5: 2 GMFC-MLD 6: 2	GMFC-MLD 2: 0 GMFC-MLD 3: 0 GMFC-MLD 4: 0 GMFC-MLD 5: 2 GMFC-MLD 6: 2	GMFC-MLD 2: 0.5 GMFC-MLD 3: 0.5 GMFC-MLD 4: 1 GMFC-MLD 5: 2 GMFC-MLD 6: 2	[redacted]	[redacted]
Time to engraftment of OTL-200					
Time to engraftment for ES-EJ cohort	6 months	0 months	12 months	[redacted]	[redacted]
Full and partial response rates associated with OTL-200					
Full responder and partial-responders stabilising at GMFC-MLD 2	Full responders: PS LI: [redacted] PS-EJ: [redacted] Stabilised partial-responders: LI: [redacted] PS-EJ: [redacted] ES-EJ: [redacted]	Full responders: PS LI: [redacted] PS-EJ: [redacted] Stabilised partial-responders: LI: [redacted] PS-EJ: [redacted] ES-EJ: [redacted]	Full responders: PS LI: [redacted] PS-EJ: [redacted] Stabilised partial-responders: LI: N/A PS-EJ: N/A ES-EJ: [redacted]	[redacted]	[redacted]
OTL-200 progression modifiers					
Progression modifiers (from GMFC-MLD 0 to GMFC-MLD 6)	Determined from comparison of progression from 2-5 in OTL-200 vs BSC patients	Progression Modifier = 3.2x for PS LI, PS-EJ and ES-EJ	Source: SEE	[redacted]	[redacted]
Distribution of subgroups in combined MLD population					
Proportion of disease variant in MLD combined population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history data source					
Source of natural history data for LI and EJ	Source: OSR-TIGET Natural history Study	Source: Elgun, 2019	Source: Kehrer, 2011	[redacted]	[redacted]

5.2.4 Additional scenario analyses requested by the ERG

At the clarification stage, the ERG noted a number of areas of uncertainty and requested that the company provide additional scenario analyses. The results of these are in Table 30.

The majority of scenarios were associated with a more conservative estimate of the ICER for OTL-200 versus BSC. A scenario that assumed that all patients would be identified while they were pre-symptomatic due to a new-born screening process was associated with a [redacted] reduction in the ICER, due to the increased proportion of full responders in these populations compared with the early symptomatic patients. The remaining scenarios were mostly associated with modest increases to the ICER; however, notably the scenario in which patients receiving OTL-200 who achieved partial stabilisation in stages GMFC-MLD 3 and 4, as described by the company's clinical experts, was associated with an increase of the ICER of [redacted].

Table 30 Results of scenario analyses undertaken at the clarification stage (combined MLD population)

Scenario	Alternative assumption	ICER
Base case analysis	-	[redacted]
Time to progression	Time to progression = 50 years for PS-LI and PS-EJ patients	[redacted]
New-born screening	PS-LI = 80% of the combined cohort; 100% Full-responders PS-EJ = 20% of the combined cohort; 100% Full-responders ES-EJ = 0% of the combined cohort	[redacted]
Increased hazards of mortality	Parametric curves based on most pessimistic survival used for mortality estimate from GMFC-MLD 6 to death (LI: Gompertz, EJ: Gompertz)	[redacted]
Equipment one-off costs	New monthly equipment costs = weighted average of 100% equipment costs in 1st month and 50% equipment costs in subsequent months based on average time spent in each GMFC-MLD health state for the BSC combined cohort. E.g. If patients spent an average of 10 months in GMFC-MLD 1, then monthly GMFC-MLD 1 equipment cost = (1/10 months * Monthly Equipment Cost) + (9/10 months * 50% Monthly Equipment Cost). Equipment cost values had to be presented as an average given that the partitioned survival model is memoryless.	[redacted]
Alternative utilities	EJ utility values reported by respondents below -0.594 were changed to -0.594.	[redacted]
Alternative utilities (rescaled values)	EJ utility values reported by respondents were rescaled into the range between 1 and -0.594. All non-negative values remained unchanged, but values between 0 and -1 were rescaled to between 0 and -0.594.	[redacted]
Alternative costs	Used averaged monthly medical costs between MLD and CLN2 Health State costs. Health states were aligned on the basis of severity (CLN2 HS2 = GMFC-MLD 1; CLN2 HS7 = GMFC-MLD 6). GMFC-MLD 0 is aligned with the gen. pop. and remained unchanged.	[redacted]
Multiple stage stabilisation	Stabilisation applied to patients in GMFC-MLD 3 and 4 based on values provided in structured expert elicitation GMFC-MLD 3 stabilisation: 14% PS-LI; 15% PS-EJ; 13% ES-EJ GMFC-MLD 4 stabilisation: 14% PS-LI; 15% PS-EJ; 13% ES-EJ	[redacted]
Increased mortality	Increased MLD-related mortality in GMFC-MLD 1-5 based on NICE ERG report on CLN2 GMFC-MLD 0 = 1.0x; GMFC-MLD 1,2 = 1.4x; GMFC-MLD 3,4 = 2.0x; GMFC-MLD 5 = 9.92x	[redacted]
Removal of LI utility assumption	LI patients utilize LI utility values for duration of model (i.e. do not switch to EJ utility values at 48 months)	[redacted]

GMFC-MLD 0 monitoring cost	1 annual inpatient hospitalisation applied to GMFC-MLD 0 patients	[redacted]
Respite care costs	Respite care included for GMFC-MLD 4 (25% utilizing for 10 days per year), GMFC-MLD 5 (50% utilizing for 30 days per year), GMFC-MLD 6 (100% utilizing for 36 days per year)	[redacted]
Long-term social care costs	Community nurse costs applied to patients 19+ years old in GMFC-MLD 1-6 Local provision care home for adults costs applied to patients 19+ years old in GMFC-MLD 3-6 (50% in GMFC-MLD 3, 100% in GMFC-MLD 6)	[redacted]
Hospice care costs	Hospice/palliative care cost (estimated at £400 per day) used to replace inpatient hospitalisation cost for GMFC-MLD 6 (Living in Hospital/Hospice) patients	[redacted]
Stabilised patient costs	Stabilised patients applied a 50% reduction in health resource utilization	[redacted]
Results generated by the ERG from the company model, the results presented by the company did not include the PAS for OTL-200. Please note, an error was detected in the model when generating the results for the scenario where the LI utility assumption was removed: this was amended by the ERG.		

5.3 Model validation and face validity check

5.3.1.1 Internal consistency

The company did not provide any details on quality checks performed on the health economic model to validate its functionality. The ERG conducted a range of checks to assess the robustness of the executable model. This included an initial examination of key calculations and an assessment of whether model predictions aligned with the supporting clinical data prior to the clarification step. This initial validation identified several calculation errors which were raised with the company. As part of the company's clarification response the company provided a revised model that addressed these errors. This model was then subject to further validation by the ERG, which included a range of black box tests, examining whether varying input parameter values would generate intuitive results; the tracking of how parameter inputs feed into the model; and, an examination of the main calculation sheets. This second validation resulted in three further errors in the executable model being identified. These errors concerned the following:

- The proportion of stabilised partial responders assumed to remain GMFC 1, which led the model to overestimate progression of these patient.
- The modelling of disease related mortality, which as highlighted in Section 4.2.7.3 used survival data from birth rather than GMFC 6.
- The application of age-related decrements to utility to children.

These issues are corrected in scenario analysis presented in Section 6.

5.3.1.2 External consistency

The company did not conduct data validation of the economic model against existing literature within the original submission. Comparisons with the external literature carried out by the ERG, however,

show that the model performs poorly, tending to overestimate both the time to end stage disease (GGFC 6) and time alive. For example, Kehrer *et al.* (2011)[22] reports that LI patients reach GMFC 6 at a median age of 33.5 months, with all patients reaching that stage by 40 months. Model predictions, however, suggest at fewer than [redacted] of patients reach GMFC 6 by 33 months. Similarly, the Mahmood study suggests that no patient with LI MLD remained alive beyond the age of 10, while the company model predicted that [redacted] of patients remain alive. Similar issues are also apparent in the EJ cohorts.

The poor external validity is a consequence of issues highlighted in Section 4.2.3.1and 4.2.7.2 , relating to the late starting age and the estimation of time spent in the GMFC 0. The error highlighted above regarding the calculation of mortality risk in GMFC 6 also contributes to the model overestimating the life expectancy of patients.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The following sections provide details of the additional analyses undertaken by the ERG to explore the key issues and uncertainties raised in the review and critique of the cost-effectiveness evidence submitted by the company. All results over the following sections are presented deterministically. This means that the associated decision uncertainty will not be represented, however, the model was not appropriately built to run probabilistic analyses. This could not be corrected by the ERG given the time constraints of the appraisal. All results over the following sections are inclusive of the submitted patient access scheme discount for OTL-200, [redacted].

6.1 Exploratory and sensitivity analyses undertaken by the ERG

1) Cognitive impairment consistently linked to GMFC score across treatment arms, i.e. no independent treatment effect upon progression of cognitive impairment

The ERG disagreed with the assumption that patients whose motor symptoms continue to decline following treatment with OTL-200 will have preserved cognitive function. It also disagreed with the company's modelling approach of modelling different base-line distributions of cognitive impairment for each treatment. As outlined in Section 4.2.2.2, there is insufficient evidence to suggest that full cognitive function will be preserved following treatment with OTL-200 and surrogate markers of disease do not align with these assumptions. The ERG therefore presents a scenario in which the same rates of cognitive function are applied in equivalent GMFC states regardless of treatment received.

2) Revised distribution of patients across MLD sub-types to better reflect epidemiological data

As discussed in Section 4.2.3.2, the ERG the modelled population includes three distinct sub populations: pre-symptomatic late infantile; pre-symptomatic early juvenile; and, symptomatic (GMFC <2) early juvenile. To estimate an ICER for the combined population (covering the whole marketing authorization) the ICERs for each group were aggregated as a weighted ICER based on the expected incidence of patients across the three groups. The results of the elicitation process used to generate the weights applied to each population demonstrate substantial divergence in clinical opinion and appear inconsistent with epidemiological evidence. The ERG therefore felt that the weights applied to each subgroup ICER should better account for the available epidemiological evidence.

The revised distribution of patients across the three populations integrates epidemiological data on the incidence of each phenotype with clinical opinion elicited as part of the OTL-200 HE Advisory board.

The assumptions informing the ERG re-analysis along with sources for each parameter are outlined in Table 31.

Table 31 Assumptions underpinning ERG's re-estimated eligible population distribution

Assumption	Source
50% of all MLD patients are diagnosed with late infantile	Mid-point of estimated proportion of late infantile patients reported in Wang *et al.* 2011.[12]
27.5% of all MLD patients are diagnosed with juvenile MLD	Mid-point of estimated proportion of juvenile patients reported in Wang et al. 2011.[12]
50 % of Juvenile patients are early juvenile	Assumption
16% of Late infantile patients are pre-symptomatic at diagnosis	OTL-200 HE Advisory board.
17% Juvenile patients are pre-symptomatic at diagnosis	OTL-200 HE Advisory board.
13% of Juvenile patients would be classified as early symptomatic	Based on the ratio of pre-symptomatic and early symptomatic patients (31/40) elicited at OTL-200 HE Advisory board.

Based on these assumptions the ERG revised proportions are as follows: 65.85% of patients are pre-symptomatic late infantile; 19.24% are pre-symptomatic early juvenile; and, 14.91% are early symptomatic early juvenile.

3) Impact of using a 3.5% discount rate on costs and effects

The company revised base-case uses a non-reference discount rate of 1.5% on the grounds that the criteria outlined in the NICE methods guide are met. As discussed in Section 4.2.6 the ERG, there to be significant uncertainty as to whether the relevant criteria are met, particularly in early symptomatic early juvenile patients. The ERG therefore presents a scenario with the 3.5% discount rate applied.

4) Relaxed assumptions around the permanence of treatment effect in all patients

The company's base-case model assumed that patients classified as functionally stabilised (full and stable partial responders) would remain stable indefinitely. For the reasons discussed throughout Section 4.2.2.4 and 4.2.7 the ERG considered it prudent to explore assumptions that relax this assumption and assume instead that the treatment effect may not be permanent in all patients due to the evidence of continuing decline seen across a number of outcome measures. The ERG therefore explored a series of scenarios where the period of which stability continues is shortened. In Scenario 4a) it is assumed that response is stable for an average of 100 years, in 4b) this revised to 50 years, in 4c) to 20 years, and finally in 4d) to 10 years. The model assumes that patients have an equal probability of losing stability at every cycle, with 50% having lost stability by year 100 of the model.

Patients who lose stability progress through the GMFC states at the same rate as unstable partial responders.

5) Responder proportions re-analysed according to IPD trajectories and consistent definition of stability – stability conditional on whether GMFC drops occurred <12 months from treatment

As discussed in Sections 4.2.2.4 and 4.2.7.1, the ERG considered it appropriate to impose a minimum period of stability before permanence was assumed. This was on the basis of a number of trial patients experiencing drops in their GMFC score after long periods of apparent stability. The ERG also considered it inappropriate to class patients as full responders with very little follow-up, and patients as functional stabilisers who had recently experienced a drop in their GMFC score after a period of stability.

The ERG therefore revised the proportion of unstable partial responders to reclassify any patient as unstable who experienced a decline more than 12 months after treatment. This was in light of the company's provided rationale behind the 'functional stabiliser' response pattern, in which patients who have manifestations of disease at baseline experience decline prior to the beginning of the treatment effect, which was stated by the company to occur by 6 months at the latest.

In Scenario 5a), patients for whom there was less than 12 months of follow-up were excluded from the analysis. This may represent an optimistic interpretation, as a number of patients exhibited much longer periods of stability (>2 years) prior to a decline in their GMFC score. Scenario 5b) assumes that two patients excluded from Scenario 5a) are unstable partial responders, as these patients [redacted] at the most recent follow-up.

These response rates were also adjusted to include the one ES-EJ patient whom the company chose to exclude from their analyses because they died during follow-up, but who was otherwise considered to meet the marketing authorisation.

Table 32 Updated response proportions

Response category	LI (Scenario 5a)	LI (Scenario 5b)	PS-EJ	ES-EJ
Full responders	[redacted]	[redacted]	[redacted]	[redacted]
Late stabilisers	[redacted]	[redacted]	[redacted]	[redacted]
Unstable	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient follow-up	[redacted]	-	-	-

6) Equal progression modifiers applied to ES/PS-EJ patients with unstable partial response

The ERG considered it inappropriate to assume EJ patients who achieve an unstable partial response would have a different disease trajectory in terms of their time spent in each GMFC state based on their symptom status at diagnosis. This scenario therefore assumes that the same set of progression modifiers are applied to pre-symptomatic and early symptomatic EJ patients who continue to decline after treatment with OTL-200.

7) Health state residence times recalculated using OSR-TIGET natural history data

The company's approach to estimating time in GMFC 0 is inconsistent with the OSR-TIGET and generates results that are inconsistent with the natural history of MLD. To re-estimate the time spent in GMFC 0, the ERG used IPD from the OSR-TIGET natural history study to calculate the average age LI and EJ entered GMFC 1. The ERG then subtracted the modelled starting age reported in the CS to estimate a mean time in state. For ES-EJ patients, the time spent in GMFC 0 and GMFC 1 was assumed to the same as in PS-EJ. This was done as more appropriate values cannot be estimated due to the significant mismatch between the EJ patients in the OSR-TIGET natural history cohort and the ES-EJ population that contributed to the integrate efficacy analysis. This results in time in GMFC 0 and 1 being overestimates for the ES-EJ population. Based on this approach, the mean time in GMFC 0 for LI patients was estimated to be [redacted] months compared with 10 months in the company's revised base-case. In the EJ sub-population, time in GMFC 0 was revised to [redacted] months compared with 58 months used in the company's revised base-case.

8) Standardised mortality ratios applied for neuro-disability and myeloablative conditioning

The following scenarios include recognition of the additional mortality risks that may be faced by functionally stabilised patients (full and stabilised partial responder). In this scenario mortality associated with lifelong neuro-disability in GMFC 1 – 5 was applied informed by values applied HST12 (cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2). Additionally, the ERG also considered it appropriate to model a small increase in long-term mortality associated with having undergone myeloablative conditioning. Consideration of the long-term effects of busulfan use on several systems was highlighted by the company's clinicians on their health economics advisory board and has been applied in the appraisal of betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia applied. An additional additive risk of 1.25 is therefore applied to all health states. Note, due to the restrictions associated with the model structure this SMR was also applied to BSC patients, however, the comparatively short period these patients spend outside of GMFC 6 meant it led to a difference of only 0.0005 in pooled BSC QALYs. The SMR's applied are listed in Table 33.

Table 33 MLD-related standardised mortality ratios (vs general population)

GMFC-MLD stage	SMR (LI & EJ)
GMFC-MLD 0	1.25
GMFC-MLD 1	1.65
GMFC-MLD 2	1.65
GMFC-MLD 3	2.25
GMFC-MLD 4	2.25
GMFC-MLD 5	10.17

9) Survival curves based on combined mortality IPD for LI and EJ patients in GMFC 6

The company updated their mortality calculations for patients in GMFC 6 to explicitly use survival data from the OSR-TIGET study in their clarification response. As discussed in Section 4.2.7.3, the ERG considered this to have been implemented sub-optimally, as survival curves were fitted to EJ and LI patients independently, despite mortality being equally likely in these patient groups once GMFC 6 is reached. The ERG therefore combined the Kaplan-Meier data for LI and EJ patients supplied by the company and fitted parametric models to predict mortality.

The Weibull function was applied to both groups as was the case in the company's model. Modelling increasing hazards over time ensures that patients are not predicted to significantly outlive their life expectancy, as was the case in the original model. Weibull is the second most pessimistic extrapolation, meaning the cost-effectiveness of OTL-200 is increased relative to all other functions except Gompertz. Fit statistics were similar for all fitted curves.

10) Alternative assumptions around impact of cognitive function upon HRQoL

As discussed in Section 4.2.8.4, the ERG did not consider there to be sufficient evidence of an additive effect of cognitive impairment upon HRQoL, particularly in patients with and already high dependence upon caregivers. In Scenario 10 a) the ERG therefore presents a scenario where no additional HRQoL decrements associated with cognitive impairment. This scenario also applies EJ utilities to LI patients to illustrate the impact of this assumption upon this population.

Evidence in other conditions as discussed in Section 4.2.8.4 suggested that the primary route through which cognitive impairment affects HRQoL is through a loss of independence and ability to perform daily living skills. The ERG therefore considers it plausible that HRQoL will be affected by cognitive impairment in patients with preserved motor function, but not in highly dependent patients with daily living and communication skills severely limited by motor dysfunction. In scenario 10 b) the utility

decrements associated with increasing cognitive dysfunction are therefore only applied health states in GMFC 0 – 2.

11) EJ utilities applied to LI patients

The company revised base-case applied the LI utility set throughout a patient's life resulting in patients with classified in notionally similar health states to be assigned very different utility values depending on whether they are in the LI or PS-EJ/ES-EJ sub-populations. The ERG disagreed with this approach and considers that the application of two separate utility set's to be overly complex and unnecessary. The ERG therefore presents a scenario in which the EJ utility set is applied in the LI sub-population.

12) Age related disutility removed from children, applied to patients across all GMFC scores

As discussed in Section 4.2.8.5, the ERG identified two methodological inconsistencies with regards to the application of age-related decrements to the modelled utilities. Firstly, HRQoL was assumed to peak at birth, with the general population trends elicited from >16-year olds extrapolated to younger patients. Secondly, utilities were adjusted for age only in patients at GMFC 0, which led to higher utilities for patients stabilising at GMFC 1 and 2. The ERG corrected these issues in line with the conventional application of age-related decrements, i.e. age-related decrements were applied only to patients within the range of the sample population, and were applied equally to all patients regardless of their GMFC score.

13) Caregiver decrements applied at an earlier stage of disease progression

As discussed in Section 4.2.8.6, the ERG considered the application of a disutility to carers only to those with MLD dependents in GMFC 5 and 6 to be poorly representative of the care burden caregivers face much earlier in the disease course. The ERG therefore implemented a revised scenario informed by advice from the ERG's clinical advisor. In this scenario the number full time carers is modified such that a full time care and supervision from at least one parent would be necessary from GMFC 2 onwards, with at least some impact upon the health and mental wellbeing of caregivers of patients in GMFC 1. The revised assumptions are summaries in

Table 34.

Table 34 Impact upon caregivers by GMFC score of MLD dependents

Health state	Number of caregivers required		
	Company base-case assumption	Company scenario	ERG Scenario
GMFC 0	0	0	0
GMFC 1	0	0	0.5
GMFC 2	0	0.5	1
GMFC 3	0	0.5	1
GMFC 4	0	1	2
GMFC 5	2	2	2
GMFC 6	2	2	2

14) Alternative assumptions around settings of care provision in GMFC 6

The ERG considered the inclusion of 7.2 hours per day of social care costs to patients in GMFC 6 whose care was primarily hospital-based inappropriate, as this level of care is already accounted for in the hospitalisation costs for these patients. In scenario 14a) the ERG therefore removes this additional cost for the 20% of GMFC 6 patients that the company assumes are cared for in hospital full-time.

Further, the ERG considered the company's assumption that 20% of patients in GMFC 6 would be treated in hospital full-time to represent a misunderstanding of the advice of patient groups and clinicians. While patients at GMFC 6 may spend 20% of their time in hospital for resolution of acute issues such as status epilepticus and chest infections, they are unlikely to require long periods of care in hospital. The model already accounts for hospitalisation due to the above reasons, it is therefore inappropriate to also model 20% of patients to be treated in hospital full time. In scenario 14 b) the ERG revises the health state costs applied in GMFC such that all patients are assumed to be cared for in a home setting.

15) Adult social care costs include institutional care

In Section 4.2.9.2, the ERG notes that resource use in adult patients is largely the same as those for children in the equivalent health state. And that this may not be reasonable and is likely, particularly as patients age that they adult patients with MLD will require support in the form of either in home social care or residential care where patients are not able to live independently. The ERG did request that the company provide a scenario at clarification to explore this, but feels that this scenario does not fully represent the care needs of patients as it largely ignores the need for residential social care. In scenario 15 the ERG therefore presents in own scenario. Assumptions made regards in-home care and residential care summarised in Table 35. Unit costs applied were sourced from PSSRU [49]and

assumed residential care costs of £1272 per week (Local authority own-provision care homes for adults requiring physical support (age 18-64)) and Day care costs of £245 per week (Day care for adults requiring physical support (age 18-64)).

Table 35 Summary of revised adult social care costs

Health state	Full time residential care	Day care
GMFC-0	0%	0%
GMFC-1	0%	10%
GMFC-2	5%	20%
GMFC-3	20%	20%
GMFC-4	40%	20%
GMFC-5	60%	20%
GMFC-6	60%	20%

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

A summary of the ERG's exploratory analyses of the cost-effectiveness of OTL-200 for the treatment of MLD is presented in Table 36. The results presented are inclusive of the PAS available for OTL-200.

Table 36 Exploratory analyses performed by the ERG

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
ERG corrected base case																
BSC	[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]
ERG Scenario 1: Cognitive decline linked to GMFC progression in OTL-200 patients																
BSC	[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]
ERG Scenario 2: Alternative MLD subtype distribution																
BSC	[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]
ERG Scenario 3: Discount rate of 3.5% for costs and benefits																
BSC	[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]
ERG Scenario 4a: Stability persists for 100 years on average																
BSC	[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]
ERG Scenario 4b: Stability persists for 50 years on average																
BSC	[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]
ERG Scenario 4c: Stability persists for 20 years on average																
BSC	[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]
ERG Scenario 4d: Stability persists for 10 years on average																
BSC	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 5a: Patients with <12 months follow-up excluded																
BSC	[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]
ERG Scenario 5b: Patients with <12 months follow up and decline classed as unstable partial responders																
BSC	[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]
ERG Scenario 6: Equivalent progression modifiers applied in ES EJ and PS EJ patient																
BSC	[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]
ERG Scenario 7: Re-analysis of OSR-TIGET health state residence times																
BSC	[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]
ERG Scenario 8: Incorporation of neuro-disability-related and myeloablative conditioning SMRs for patients in GMFC 1-5																
BSC	[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]
ERG Scenario 9: Updated survival models based on pooled LI/EJ data in GMFC 6																
BSC	[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]
ERG Scenario 10a: HRQoL determined only by GMFC score (no independent effect of cognitive impairment)																
BSC	[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]
ERG Scenario 10b: Cognitive impairment decrements applied only in GMFC 0 – 2																
BSC	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
OTL-200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 11: EJ utilities applied to LI patients																
BSC	[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]
ERG Scenario 12: Age adjustments removed from patients aged <16 and applied to all patients regardless of GMFC stage																
BSC	[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]
ERG Scenario 13: Caregiver decrements applied at an earlier stage of disease																
BSC	[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]
ERG Scenario 14a: Additional costs of social care removed from hospitalised patients																
BSC	[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]
ERG Scenario 14b: Assume all patients in GMFC 6 are cared for primarily in a home setting.																
BSC	[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]
ERG Scenario 15: Adult social care costs include institutional care																
BSC	[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]

6.3 ERG's alternative base-case analysis

The ERG's alternative base-case analysis combines a number of the above scenario analyses. This includes Scenarios 1, 2 (affects pooled ICER only), 3, 5a, 6, 7, 8, 9, 10a, 11, 12, 13, 14b, 15. The ERG considers this new analysis to better represent the trial data, and to address some of the ERG's concerns around the assumptions used in the company's base-case analysis. This analysis also reduces the impact of internal inconsistencies and uncertainties around the utility value set. The results of the ERG base case are presented in Table 37.

Table 37 ERG's preferred model assumptions

Population	Intervention	Total			ICER
		Costs (£)	LYs*	QALYs	
PS Late Infantile	BSC	[redacted]	[redacted]	[redacted]	-
	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]
PS Early Juvenile	BSC	[redacted]	[redacted]	[redacted]	-
	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]
ES Early Juvenile	BSC	[redacted]	[redacted]	[redacted]	
	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	BSC	[redacted]	[redacted]	[redacted]	
	OTL-200	[redacted]	[redacted]	[redacted]	[redacted]

6.3.1 Scenarios on the ERG alternative base-case analysis

The alternative set of assumptions and data applied in the ERG's alternative base-case analysis represent a better use of the available evidence, however, a number of important uncertainties remain. To illustrate the effect of these uncertainties upon cost-effectiveness estimates, the ERG conducted a number of scenario analyses based on the ERG's base-case as described in Section 6.1.

The first of these scenarios included the use of a 1.5% discount rate for costs and benefits, which was originally applied by the company in their base-case analysis. The ERG considers that a discount rate of 3.5% remains the most appropriate for the reasons discussed in Section 4.2.6, but presents this analysis to permit comparison of the company and ERG preferred analyses.

In the second set of scenarios, the ERG considers the impact of alternative assumptions around the permanence of the treatment effect. As previously discussed, the ERG does not consider the biological plausibility of a long-term treatment effect associated with OTL-200 to be sufficient evidence that loss of efficacy is implausible. The evidence discussed in Section 4.2.7.1 suggests that some stabilised patients may lose their response over time. These scenarios illustrate the very

substantial effect upon decision uncertainty when the assumption of a permanent treatment effect in all stabilised patients is relaxed.

The third scenario explores the implications of applying the distribution of stabilised patients across GMFC states as suggested by the company's advisory board. This is equivalent to the company's Scenario in response to Question B4 in their clarification response (see Section 5.2.4). This is implemented to explore the uncertainty surrounding the classification of partial responders as either unstable or stabilising at lower GMFC scores.

Fourthly, due to the significant issues with the elicitation methods used to generate the applied utility set the ERG the impact of applying the LI utility set to all patients throughout the model instead of the EJ utility set. The LI set many of the same weaknesses as the EJ utility set, but is as reasonable as the EJ utility set given the absence of alternatives.

Results for all four sets of scenarios are presented in Table 38.

Table 38 Exploratory analysis on the ERG base-case

Scenario	PS Late Infantile				PS Early Juvenile				ES Early Juvenile				Pooled			
	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER	Costs (£)	LYs	QALY	ICER
ERG Base-case																
BSC	[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]
ERG Base-case Scenario 1:1.5% discount for costs and benefits																
BSC	[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]
ERG Base-case ERG Scenario 2a: Stability persists for 100 years on average																
BSC	[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]
ERG Base-case ERG Scenario 2b: Stability persists for 50 years on average																
BSC	[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]
ERG Base-case ERG Scenario 2c: Stability persists for 20 years on average																
BSC	[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]
ERG Base-case ERG Scenario 2d: Stability persists for 10 years on average																
BSC	[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]
ERG Base-case Scenario 3: Apply LI utility set to EJ patients																
BSC	[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]

6.4 Conclusions of the cost effectiveness section

The company developed a de novo economic analysis to appraise the cost and benefits of OTL-200 for the treatment of MLD in pre-symptomatic late infantile, pre-symptomatic early juvenile, and early symptomatic early juvenile patients. This population aligns with marketing authorisation and population covered by the NICE scope. The comparator considered in the economic evaluation was BSC consisting of palliative supportive care. In contradiction of the NICE scope, haematopoietic stem cell transplant was not considered as a comparator in the economic analysis. The model structure developed was based on a multi-state Markov model approximating a partition survival model and included eight health states defined by the GMFC-MLD clinical rating scale used to assess gross motor function. To reflect the fact the MLD impacts upon cognitive as well motor function, patients in each of the GMFC health states were classified into one of three cognitive function sub-states describing the absence or degree of clinical impairment. Following revisions made to the company's base-case analysis the cognitive sub-states were restricted to the pre-symptomatic and early symptomatic early juvenile sub-populations.

To reflect that the fact the model considers three sub-populations, result of the cost-effectiveness analysis were presented for each sub-population separately as well as using a pooled ICER based on a weighted average of the ICERs for each sub-population. In the company's revised base-case economic analysis the ICERS for the PS-LI, PS-EJ and ES-EJ sub-populations were respectively [redacted], [redacted] and [redacted] per QALY gained. The pooled ICER was [redacted] per QALY gained. In all individual populations and in the pooled analysis undiscounted incremental QALYs exceed 30, implying a threshold of £300,000 per QALY gained as outlined in the HST interim methods guidance.

6.4.1 Conclusions of ERG's Critique

The ERG identified large number of substantive issues with the company's base-case that centred principally on the parameter values applied in the model and the company's interpretation of the limited evidence on the effectiveness of OTL-200. These issues covered all aspects of the modelling including the effectiveness of OTL-200, the effectiveness of BSC, the HRQoL values applied in the model and the care costs applied.

In terms of there likely impact on the ICER the most of these issues centre on the effectiveness of OTL-200 and classification of patients as either full responders, stabilised partial responders or unstable partial responders. The classification of patients into these three response types is highly influential in terms of the ICER, but is informed by very limited data and highly subjective given the limited follow-up and difficulties of distinguish between slowed progression and true stabilised disease. Moreover, while there is a reasonable biological rationale for the distinction between these

three categories, there is limited evidence from trial participants that justify this distinction. This is particularly the case in terms of the distinction between stable and unstable partial responders, where there are appear to be few patients that would meet the criteria for being a stabilised partial responder (initial decline followed by long-term stabilisation).

The ERG also has very substantive concerns regarding the health state utilities applied in the company's economic model. There are serious flaws in the non-reference case elicitation study used by the company to generate the applied utility set and significant evidence of bias. As a result, the applied utility values make extensive use of negative utility values that imply extreme suffering in patients with late-stage disease and limited cognitive function. The ERG takes issue with use of such strongly negative utilities, which fall well below the lowest utility ascribed to the worst health state as valued by the UK general public and while the ERG appreciates the particular difficulties associated with living with MLD, considers that the applied values to lack face-validity.

In addition to concerns about specific parameter values applied in the model the ERG has also identified broader concerns that relate to the claimed benefits of OTL-200 and the decision problem addressed by the company. The most important of these relate to the omission of HSCT as a modelled comparator, the assumed equivalence of the cryopreserved formulation, the long-term uncertainties associated with the OTL-200 and the characterisation of stabilisation as equivalent to complete cure.

As noted above the model only considers BSC as comparator and does not include HSCT as a comparator despite its listing the NICE scope and clinical opinion stating it is used in the NHS. This has important implication for the model given the likely significant overlap between the patient group eligible for HSCT and those eligible for OTL-200. Assessing the impact of this omission was not possible, but it is clear from the evidence identified by the ERG that HSCT can be effective in slowing progression of disease and improving overall survival.

The assumed equivalence of the cryopreserved formulation is also a very important issue that cannot be readily parametrised or explored in the economic analysis given the minimal data available. All the clinical data used in the economic model relates to use of the fresh form. And as discussed in the clinical section there is a suggestion that cryopreserved formulation is less effective than the fresh formulation. If the potential lack of effectiveness manifests itself in terms of either fewer patients achieving stabilisation or reduced durability of stabilisation, it will have very substantial consequences for the cost-effectiveness of OTL-200 increasing the ICER substantially.

The very small samples, necessary dissection of the available data and short-follow up also have important implications in terms of the predicted cost-effectiveness estimates. Assumptions around the durability of stabilisation, as modelled in both the company's and ERG base-case, assume that the

benefits of OTL-200 will be highly durable and persist for the life time of the patient. There is however, little direct evidence to inform this assumption and generally a lack of clinical experience of the gene therapies such as OTL-200. In this regard, the ERG highlights issues raised by the EMA relating to gene silencing and unequal attrition of high VCN cell lines which could lead to uncertainties with regards to sustained long-term efficacy. Management of these uncertainties for the NHS is important and the ERG points the committee to recommendations made in Hettle et al. regarding the use of managed access schemes and other risk sharing devices that may help to mitigate the risks of implementing regenerative technologies in the NHS.[46]

The ERG also takes issue with the company's characterisation of stabilisation which is considered by the company to be akin to cure resulting in the resolution or/and prevention of all manifestations of disease. There are substantive uncertainties regarding this assumption including important evidence on progressive peripheral neuropathy as well evidence on other surrogate markers of disease. The limitations of the current evidence base both in terms of the length of follow- up, but also importantly the breadth of outcomes assessed, makes characterisation of disease beyond gross motor skill difficult. These non-gross motor function manifestations may, however, be of substantive importance in terms of assessing the benefits of OTL-200 and are not currently reflected in the economic analysis.

In section 6 the ERG has attempted to explore the impact of the uncertainties discussed in the ERG's critique of the model. The results of this illustrated that several of the ERG's alternative assumptions impacted significantly on the results of the economic analysis. Specifically, assumptions made around the permanence of stabilisation, the proportion of stabilised patients and the discount rate applied. In the ERG base-case the respect ICERs for the LI, PS-EJ and ES-EJ were [redacted], [redacted] and [redacted] per QALY gained. In the pooled population the ERG's base -case analysis results in an ICER of [redacted] per QALY gained. These results are inclusive of the PAS discount for OTL-200.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

OTL-200 for treating metachromatic leukodystrophy [ID1666]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Tuesday 2 March** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Summary of key issues identified within the ERG report

Orchard Therapeutics would like to bring to the Evaluation Committee's attention the key issues identified in the ERG report. However, we would initially like to flag our disappointment at the approach and tone the ERG has taken in a number of key areas. The assertations made by the ERG at times are unsupported, misleading and goes against the available evidence base. Despite engagement in advance with the ERG to explain these issues and a very comprehensive MLD clinical expert summary (n=6) consisiting of the majority of MLD treating experts in England, submitted along with this dossier, the ERG have chosen to ignore this evidence and made a number of sweeping statements throughout the report without any apparent evidence to support. Whilst Orchard recognises that like most submissions, the evidence does have some limitations, especially because of the ultra-rare nature of the condition that OTL-200 treats, it is still concerning.

Orchard recognises the importance of an impartial and critical review to this process, however some of the assertations made by the ERG are completely contrary to the treating clinical expert community and PAGS expertise and most importantly are misleading and incorrect. Furthermore, as discussed below, the ERG also appears to use approaches which lack empirical evidence and concerningly criticises accepted methodology outlined in the NICE reference case whilst alternatively proposing its own methodology. For example:

- The ERG report gives an unfairly scathing account of the utility study undertaken to generate utilities, concluding that it has deep concerns with respect to the study methodology and face validity of the resulting values without presenting supporting evidence to back up its perspective. Specifically the ERG report wrongly asserts that the utility study:
    - does not reflect the lived experience of patients with MLD, ignoring the fact that Vignettes used in the study were based on caregiver interviews and clinical expert advice and recognising that direct interviews with patient would not be feasible given their young age and cognitive deficit.
    - goes against the NICE reference case, despite the fact the NICE reference case specifically states that Vignettes can be used where EQ-5D values are not available or appropriate, and that this approach of directly eliciting utilities using TTO from members of the public has been accepted by NICE in other technology appraisals (e.g. appraisal of Ranibizumab Pegaptanib for the treatment of Age-related macular degeneration (TA155)
    - was not done using the composite methodology, despite the utility study report clearly showing this methodology was used. Orchard considers that the ERG may have misunderstood the report and/or the response to the clarification question, as the correct composite TTO methodology was performed (standard and lead time to account for states worse than death).

- generated utility values lack face validity as several of the health states values were inconsistent with the lowest utility ascribed to the worst health state EQ-5D health state as valued by the UK general public, which is a clear exaggeration as only two out of the 24 health states were valued worse than the worst value generated by the EQ-5D (-0.594). To imply these results lack face validity, fails to acknowledge the wide body of evidence which have highlighted the limitations of the EQ-5D incapturing the impact conditions such as cognitive impairment, loss of vision, seizures, and incontinence have on HRQoL, and as such the lowest values based on the EQ-5D-5L cannot represent the worst health state possible.
- had 'significant bias' or "framing effect" issues, but makes these postulations without providing any empirical evidence to support this. For e.g. the ERG critiques the 10 year time horizon used in the TTO, which is the time frame used in nearly all TTO studies to estimate utilities for the EQ-5D, and proposes a 1 or 5 year tradeoff, with no evidence to show why this is more appropriate or acceptable.

- Despite overwhelming evidence from the literature, MLD caregivers, PAGs and clinical experts to the contrary, the ERG rejects the view that cognitive impairment and non-motor related neurological impairments have a distinct and measurable impact on the health-related quality of life for patients with MLD beyond the impact motor impairments. For purposes of clarity, Orchard is not proposing that the impact on quality of life of cognitive impairment is wholly additive to that of motor dysfunction, but believes that certain aspects are distinct and do not entirely overlap. Loss of cognitive function limits communication and social relationships between children with MLD and their family, and it will limit enjoyment of life. In contrast children with very severe neuromuscular conditions but with intact cognitive function are often described as happy or joyful children because they maintain enjoyment of life and social interactions. Therefore, for the ERG to conclude that a patient with a GMFC score of 3 (unable to walk) but who has (i) no problems in remembering things, (ii) is able to concentrate on tasks , and (iii) is able to learn new skills; has the same HRQoL to a patient who also has a GMFC score of 3 but who is very limited in their ability to communicate and who has minimal ability to learn new skills goes against the evidence base.

- The ERG state that advice received from its one clinical expert confirmed the use of HSCT in the NHS for the treatment of late infantile (LI) and early juvenile (EJ) MLD patients and that there would be significant overlap between the patient group eligible for HSCT and those eligible for OTL-200. This is simply not the case and may represent a misinterpretation of the clinical expert opinion received. There is clear expert EBMT / BSBMT clinical guidelines, PAG testimonials and several clinical experts contrary evidence to indicate that HSCT would not be considered in LI patients or early symptomatic EJ (ES-EJ) patients, which together accounts for over 80% of the eligible patient group. For the 20% of patients who may be theoretically eligible for HSCT (i.e. pre-symptomatic EJ (PS-EJ) MLD patients), the difficulties and delay in finding a suitable donor match as well as the considerable risk of graft vs host disease (GvHD), which is particularly high in patients with MLD, and other complications including acceleration of disease progression, severely limits the use of HSCT, even in the PS-EJ group. Expert advice has confirmed that HSCT it is not used routinely in clinical practice, even in this small group of MLD patients. In the UK, decisions regarding the use of HSCT where it has not been specifically indicated are made by a national multi-disciplinary team involving experts across the country who discuss the use of HSCT in metabolic conditions. In the 15 years that the clinical expert has been a member of this MDT, *no* early juvenile MLD patient has been given HSCT even though some clinicians may have considered it.

- The ERG argues that in the ES-EJ sub-population a patient was inappropraitely excluded from the analyis as they received treatment and would be otherwise eligible under the marketing authorisation. As a result, this exclusion leads to the proportion of stable partial responders being overestimated. However, this is not the case. EMA studied the whole dataset and accepted this type of patient would be ineligible, and agreed on very specific wording in the SmPC regarding eligibility to cover this type of patient in the future including the requirement for "physicians to check that the patient hadn't declined and is still clinically appropriate". As mentioned in the company submission this rationale was informed by analysis of treatment failures to identify baseline predictors of treatment benefit. This patient was borderline at baseline (IQ = 87 and GMFC 1) and had a significant decline in gait (walking ability) between screening and baseline (prior to conditioning). The SmPC clearly warns that patients should not receive Libmeldy if they have clinically deteriorated as this is an indication they are entering the rapid progressive phase of the disease. Furthermore, the company sought the opinion of UK MLD clinical experts regarding this specific patient in both an advisory board setting and a follow up to the ERG report to ascertain whether they would be treated in real clinical practice. The information received categorically states that clinicians would align with the SMPC and not treat this type of patient. Orchard feel it is remiss for the ERG to ignore both the EMA determination of the final license and several treating clinical experts in the UK that were specifically asked this question and confirmed that this would be in line with their clinical practice.

ERG response

The ERG notes concern regarding the content of the ERG report and the critique of the company submission. The ERG would, however, like to reassure the company and the committee of its impartiality and that its priority is to ensure that new healthcare technologies represent value to the NHS. In this regard, the ERG has sought to support the company to provide appropriate information and justification for their approach and has shown significant flexibility in accommodating several deviations from the usual appraisal process, including agreeing to a substantial extension to the clarification process and additional teleconferences.

The ERG disagrees that the specific points raised by the company as part of Issue 1 represent factual inaccuracies, but rather considers these areas of disagreement between the company and the ERG. The ERG therefore does not respond to the issues raised above here; instead, please refer to our response to each issue in the tables below. The ERG would also like to highlight that most of the issues raised by the company were not considered to be factual errors by the ERG. In only small minority of cases was the ERG required to delete whole sentences, which was the proposed amendment in the vast majority of the factual inaccuracy issues raised by the company.

Issue 2 Utility study methodology and alignment with NICE reference case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 table row 16. The report states: "*The study adopted an approach inconsistent with the NICE reference case*."	The company suggests that this statement is deleted in its entirety.	It is factually inaccurate to state that this was inconsistent with the NICE reference case, which clearly indicates that Vignettes can be used where EQ-5D values are not available or inappropriate. Given the significant cognitive impact of MLD it is clear using EQ-5D in a condition like MLD would be inappropriate as it would not capture the impact of cognitive impairment that is not mediated through impact on usual activities, anxiety or self care.	Not a factual inaccuracy. The statement is correct. Section 5.3.4 of the NICE Reference Case should be interpreted in the context of 5.3.5 to 5.3.11, which states that for the sake of consistency across appraisals, EQ-5D is the preferred value set for

		There is also precedent for NICE accepting studies in which utilities were elicited directly from members of the public using TTO. One example is in the technology appraisal of Ranibizumab Pegaptanib for the treatment of Age-related macular degeneration (TA155), the NICE appraisal committee accepted utilities elicited from members of the public by time trade-off because the EQ-5D was deemed inappropriate as it doesn't capture impact of vision on patients.	public preferences. Section 5.3.10 Reference Case provides details of the type of evidence that must necessarily accompany deviations from NICE's preferred methods. This has not been provided by the company. For clarity the text in the ERG Report has been amended to the following: "The study adopted an approach inconsistent with the preferred methods described in the NICE reference case, and preferable alternatives. The company provided insufficient justification for this deviation".
Page 15 table top row. The report states: "*This means patients in essentially the same health state are assigned different utility values depending on whether they are in the LI or EJ sub-population*.	Suggest this statement is deleted entirely.	This is not factually correct as the average EJ utility is roughly equivalent to LI utilities. For example, the average utility across the three cognitive substates of GMFC 6 is -0.51 which is similar to the utility for LI patients which is -0.47	Not a factual inaccuracy. No revision made. This is a rather selective example. The utility values applied differ substantially across many of states. The statement also does not

			make any reference to the size of this difference, only that they are different which as the Company response acknowledges is in fact the case.
Page 15 table row 18. The report states: " *There is evidence to suggest significant bias in the elicitation study regarding the impact of cognitive impairment*.	Either delete in its entirety or rephrase to "the approach to capturing the impact of cognitive impairment in the elicitation study may have some bias"	Factually inaccurate to say there is evidence. The ERG makes this inference without providing any empirical evidence to back up the statement. Rather the ERG provides only speculations on why the approach maybe biased. Whilst the company appreciates the ERG may disagree with the approach the company undertook, the suggestion that there is significant bias has not been proven as such the statement should be deleted or rephrased so it doesn't provide a misleading perspective.	Not a factual inaccuracy. No revision made. The ERG Report provides numerous examples of results from the elicitation study, i.e. evidence, which are suggestive of bias.
Page 15 table row 18. The report states: " More generally the utility values applied in several health states are inconsistent with the lowest utility ascribed to the worst health state EQ-5D health state as valued by the UK general public. "	Please can you be more specific i.e. say "*the utility values applied* in 2 of the24 health states *are inconsistent with the lowest utility ascribed to the worst health state EQ-5D health state as valued by the UK general public"*	This is factually inaccurate as only 2 of the 24 health states had values below the lowest EQ-5D levels of -0.594. These two health states are GMFC 5 (severe cognitive impairment) and GMFC 6 (severe cognitive impairment) with utilities of -0.72 and -0.80. All other health states were above -0.594. Moreover the statement goes against the plethora of evidence that has shown that the EQ-5D does not capture the impact of cognitive impairment (Oremus et al 2016[4]),	Text revised to the following: *"More generally, the utility values ascribed to two health states are inconsistent with the lowest utility ascribed to the worst EQ-5D health state as valued by the UK general public. The vast majority of*

		vision loss (Sampson et al 2019[6]), and limitations in social interactions on quality of life (Sampson et al 2019), and as such the lowest values based on the EQ-5D-5L cannot represent the worst health state possible.	*BSC patients [redacted] are ascribed the worst utility for much of their lives."*
On Page 118, it is stated that: '*The company stated that the time trade off (TTO) exercise was based on the 'composite TTO' methods as described by Oppe et al.[28] However, in the description and TTO script provided in response to clarification, the ERG could not verify that composite TTO was used. Instead, it appeared that conventional TTO and lead-time TTO were administered independently, an approach which has been superseded due to the severe framing effects observed using this method.[28]* *In their clarification response, the company indicated that in participants who rated the health state as worse than death on the VAS task, lead-time TTO was used instead. It appeared that the interviewer initiated the lead-time procedure immediately, rather than adopting the standard composite TTO approach in which participants work through trading off their initial allocation of 10 years first. In their*	Amend paragraph to reflect that correct methodology was performed.	This is incorrect. The standard time-trade off method was completed for all states which were better than dead, and lead time method was adopted for those that were worse than dead. In the time trade-off task, participants started all states using the conventional method. The VAS task did not set the precedent for the lead-time task for any health state, even if a participant rate a state as worse than dead in the VAS task. The lead time method was used for a health state when participants were presented with all options for full health and then believed that the state was worse than 0 years in full health. At this point, lead time method was adopted. Therefore, the utilities elicited could range from -1- +1.	Not a factual inaccuracy. The methods used by the company remain unclear. If the methods described in the PFC response are incorrect, the company should clarify why this was the case. Janssen *et al.* describes a process in which conventional TTO is first administered all participants to determine whether they consider a health state better or equal to death. The PFC response provides a detailed description of the company's methods, which appear at odds with composite TTO methodology, stating: *"If a vignette was rated as*

clarification response, the company described a procedure where a different TTO exercise was undertaken based on the outcome of the VAS task, rather than first establishing whether participants expressed indifference towards 10 years of life in the health state and immediate death, in the standard TTO exercise. This meant that the utilities elicited from these participants were bounded at -1 and 0, with no positive values possible.' This whole paragraph is inaccurate as the composite TTO was used and the the utilities elicited for the WTD states were bounded at -1 and +1			*worse than 'dead' in the VAS task then the interviewer would turn to the procedure for states considered worse than dead. For such states the lead-time TTO (LT-TTO) valuation procedure was used."* Given the contradictory descriptions of the methods the ERG has revised the text to read as follows: *"The methods used in the time trade off (TTO) exercise were not fully clear with contradictory descriptions provided by the company. In the CS it was stated that the TTO exercise was …"*
On Page 119, the report states that "*The company stated that: Mean time trade off values for the late infantile health states were not adjusted prior to implementation in the model (see* ***Error! Reference source not found.****). However, presumably* ***due to the*** ~~***numerous***~~	Delete numerous.	Although there were few (not numerous) inconsistencies the impact was minor and did not change the general trend which showed that cognitive impairment and motor impairment are drivers of quality of life.	Revised as suggested

apparent inconsistencies *in mean TTO values generated by participants for early juvenile health states, the company used a linear regression model to predict EJ utilities on the basis of GMFC and cognitive function*.". The comment numerous inconsistencies is factually inaccurate			
Page 120-122 It is stated that "*In adopting this method, the company have not only failed to acknowledge the lived experience of patients and caregivers, but have applied a value set in which many states lie significantly outside the range of established UK public preference weights*".	Delete sentence.	There are no established UK preference weights for health - there are only weights for specific measures such as EQ-5D. Much research has shown (some of it sponsored by NICE) and endorsed by the EuroQol Group that the EQ-5D has measurement blind spots. It doesn't measure: 1. Cognitive function 2. Communication limitations 3. Vision & hearing loss 4. The impact of seizures 5. The impact on incontinence Furthermore, as stated in the company submission and the response to clarification questions, the vignettes captured the lived experience of the pateins and caregivers as they were developed based on transcripts from the interviews carried out in the caregiver survey. Finally as mentioned above, it is inaccurate to	The ERG has edited to make it clear we are referring to EQ-5D preference weights. Amended text "*established UK EQ-5D preference weights"*

		state that many states lie significantly outside the range of UK preference weights, as this applied to only 2 out of 24 health states.	
On page 121, it states "*The EQ-5D tool is widely validated in many patient populations, and preference weights have been carefully constructed for the UK population through high-quality research."* And "*No such evidence was presented by the company to justify the methods used in the present appraisal"*. This is factually inaccurate, as the company did justify why the vignette approach was taken.	Amend to, "The company justified the methods used in the present appraisal, but the ERG disagrees with them."	The ERG argue that the company should have specified that the health states were for children, and strongly propose the use of the EQ-5D. Yet, the EuroQuol group state that EQ-5D value sets cannot be used for children because health states are valued differently when ascribed to an adult or child. EuroQuol's assertion for this is based on results of an analysis by Kind et al 2015, where in a total of 1085 questionnaires completed a near-uniform pattern was found across all three countries (England, Germany and Spain) in which health state values for children were found to be lower than for adults. This is another reason why the age of the patient was not included in the vignette study.	Not a factual inaccuracy. No revision made. The ERG accepts that there may be good reason to deviate from the reference case as outlined by the company above. The company, however failed to make any meaningful case for this in the CS. Further, NICE list a number of preferable alternatives including using EQ-5D on caregivers and carers, which the company did not do, or justify not using.
On Page 122, it states that: "*the vignettes make little attempt to provide context for the symptoms they describe*." This should be deleted as not consistent with health valuation research and NICE's own guidance.	Detete sentence.	Vignettes very rarely provide context regarding diagnosis or age. Recent guidance from NICE (CHTE Methods Review: Health Related Quality of life Task and Finish group) on vignette methods states that vignettes should focus on describing relevant aspects of HRQL. As for context they state: "The inclusion of .. disease labels, symptoms, burden of disease and disease history differs	Not a factual inaccuracy. No revision made. The ERG recognises the referenced guidance. The This point should, however, be read in the context of the wider critique of the use of TTO to elicit a value set that would be applied to

		from EQ-5D .. and …the inclusion of any additional aspects within a vignette should be considered carefully, and wherever possible excluded."	very young children.
Page 122 "*the vignettes describing late infantile health states do not mention that they are imagining the life of a young child who is likely to still be early in their development of mobility and communication*." Health valuation research is designed to weight HRQL and so should be age independent. This relates to a "QALY is a QALY" concept.	The criticism that the health states are not age specific and should be deleted.	In valuation research there is no reason to request that TTO respondents consider that the vignettes describe patients of a specific age, gender or ethnicity – this is done in no other context. Also stating that the vignettes describe a young child will introduce framing effects, and bias as participants make judgements about the value of childs life. Lastly the TTO task asks you to imagine 10 years of life in a state which also doesn't work if we tell participants what age the vignette represents.	Not a factual inaccuracy. No revision made. See previous response.
Page 122, the discussions of adult versus child perceptions of health seems to suggest that the ERG think pre-school children should have been completing the TTO exercise in order to generate data regarding "pre-schooler's perception of their life". Please clarify.	Please can you clarify if possible or remove if not.	There is no research to back up the suggestion here so this needs to be clarified.	Not a factual inaccuracy. No revision made. The ERG in no way suggests that values should have been directly elicited from pre-school children. Rather we have said that the vignettes interpreted from an adult's perspective with no age context represent something very different to how a pre-schooler would feel about reduced ambulation, reduction in

			communication skills etc.
On Page 122, it states that "*While the company stated that the vignettes were reviewed by clinical experts, it remains unclear this feedback was represented in good faith in the descriptions*." This is a negative assertion that is unsubstantiated and should be deleted.	Please delete this statement.	The feedback from the advisory panel was taken as a collective. Several experts were interviewed and where a consensus view was reached this was adopted. It is not clear why the ERG have taken such very negative tone without evidence and suggestion this was not represented in good faith. Orchard would be clearly criticised for not engaging and collecting relevant expert clinical input. Where we have done so with a very robust independent SEE methodology, it is claimed that it is unsubtantiatied and not gained in good faith which is a very strong and unnecessary position and again factually inaccurate.	Not a factual inaccuracy. No revision made. The ERG Report provides specific examples of relevant testimony and feedback from the company's clinical experts that was not reflected in the vignettes. For the EJ vignettes, three clinicians were interviewed. The neuropsychologist provided specific advice around the psychological aspects of cognitive impairment which appears to be at odds with the vignette description.
On Page 122, it states that "*Participants consistently rated the milder (according to TTO) GMFC 1 (34.64) and GMFC 2 (18.96) health states (normal cognition) as being much worse than GMFC 3 (70.52) and GMFC 4 (61.79). They also rated GMFC 5 + MCI as being worse than death (-0.68), but gave GMFC 6 + MCI an average VAS score of 34.46.*	Please amend with corrected data.	The company thanks the ERG for identifying these inconsistencies which was due to a transcribing error in the reporting. The correct values are presented in Table 1 at the end of the document. This shows that there is consistency between mean VAS scores and TTO scores. Participants also rated GMFC 1 (77.35) and GMFC 2 (59.85) health states (normal cognition) as better than GMFC 3	Revisions made to remove reference to VAS scores due to company's reporting errors. The critique point remains, as inconsistencies between TTO values still stand. "There is more general

Due to the conceptual simplicity of the VAS method and the lower relative standard deviations around each mean VAS value, these scores are likely to be a better indicator of the participants' perceptions of the health states as described to them. This further demonstrates that participants were likely to have misunderstood the health states and the TTO exercise itself, or were not equipped to do so by the vignettes provided." This factually inaccurate as the inconsistencies were as a result of transcribing errors and should be updated.		(34.65) and GMFC 4 (18.97). This also shows consistency between the VAS and TTO scores and therefore that they understood the health health states regardless of the task at hand.	evidence that participants had difficulty distinguishing between the health states. For example, participants assigned a higher mean TTO utility to GMFC 2 + SCI ([redacted]) than to GMFC 1 + SCI ([redacted]), and GMFC 6 + SCI was rated better ([redacted]) than GMFC 5 + SCI (-[redacted]). Unfortunately, comparisons with VAS could not be made due to numerous reporting errors in the utility study."
Page 123 – The ERG also considers the time horizon of the TTO task to be potential source of bias. For states worse than death, participants are to imagine being in the health state for 10 years after a period of 10 years in full health.	The suggestion that this is a source of bias should be deleted.	All time horizons will influence the resultant TTO weights. Ten years was chosen in the current research to be consistent with EQ-5D established methodology. Changing the time horizon to 1 year or 5 years will have introduced bias. The fact that health states are not experienced by patients for this long is irrelevant because the valuation task is only valuing HRQL.	Not a factual inaccuracy. The ERG Report suggests that the use of a 10-year time horizon may have introduced bias for the reasons discussed.
Page 126 states "it appeared that different approaches were taken to elicit positive and negative utilities in spite of the company's described methodology"	Orchard suggests that this sentence is deleted.	The composite TTO, which was used in this study, is designed to use different approaches for positive and negative utilities. This seems to be a misunderstanding of how composite TTO works. A description of the composite TTO method by Janssen and colleagues,	Not a factual inaccuracy. As previously stated, the methods used in the TTO exercise remain unclear and

		clearly shows that the composite TTO method combines a conventional TTO to elicit values for states regarded better than dead and a lead-time TTO for states worse than dead (Janssen et al 2013[5]).	the ERG has revised the text to acknowledge this uncertainty.

Issue 3 Cognitive function and non-motor related impairments (modelling approach and impact of libmeldy)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 90 it states, "*suggesting that 2/6 (33%) of patients in the LI cohort had experienced mild cognitive impairment at 3 years*." Incorrect number.	2/15 (13%)	Should be 2/15 patients based on the whole LI data set.	Not a factual inaccuracy. No revision made. This is factually accurate for the time point described.
Page 127 it is stated: "*The very severe effect of cognitive impairment upon utility estimates reflects only public perceptions of cognitive impairment, and not how a patient with cognitive impairment feels themselves*."	This should be deleted.	The process of valuation by TTO is designed to elicit public perceptions of the severity or impact of a health state. Therefore this is not a reasonable criticism of the work and should be deleted.	Not a factual inaccuracy. No revision made. While the company are correct that this is the aim of the TTO exercise, this point reflects a critique of why TTO is not appropriate and therefore is a valid criticism of the company's approach.
Page 127 it is stated that our states: "lack face validity when compared with established	This should be clarified and referenced.	No research is cited to support this claim. If this is established clinical understanding then it must be supported by a sound body of research. Please cite it.	Not a factual inaccuracy. We have, however, revised the text to add the references

clinical understanding of the interaction between cognitive and physical aspects of health"			previously referred to in this section
typPage 127 it is stated "*and suggests the exercise is biased by social attitudes towards a loss of cognitive capacity, reflecting the participants' feelings towards a loss of their own personhood, rather than imagining themselves in the life of a child with cognitive impairment*."	This should be deleted.	The TTO exercise is designed to capture social preference weights. If people state a preference to avoid loss of cognitive function that is not a bias, it is their view. We think most people would prefer to avoid loss of cognitive function as this has a disproportionate impact on quality of life.	Not a factual inaccuracy. No revision made. As above this is valid criticism of the TTO exercise.
Page 127 it is stated "*The ERG questions the validity of the position that a child with very limited cognitive function would have a worse perception of their own quality of life than a child who is fully aware*."	This should be deleted	A child with very limited cognitive function may not perceive their quality of life accurately, but that does not mean that this loss of cognitive function is of no value or relevance. Loss of cognitive function will limit communication and social relationships with their family. It will limit enjoyment of life. In contrast children with very severe neuromuscular conditions with intact cognitive function are often described as happy or joyful children because they maintain enjoyment of life. Ekman et al (2007)[9], conducted a TTO study in dementia in Sweden. They found that mild cognitive impairment had a	Not a factual inaccuracy. No revision made. The ERG position is not that cognitive ability has no impact on HRQL per se. Instead, the ERG considers that in the context of MLD and its severe impact on a patient's life, cognitive impairment may have limited impact on HRQL.

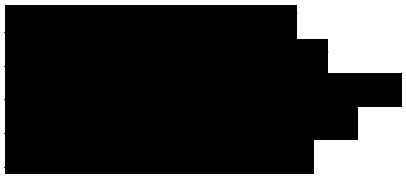
		value of 0.82 and moderate and severe dementia had values of 0.40 and 0.25 respectively. They showed that average time trade-off values declined sharply from mild cognitive impairment to progressing stages of dementia	
Page 127 also states that "*The assumption of an additive relationship between motor dysfunction and cognitive capacity is not supported by evidence across a wide range of conditions, … It has been established in numerous studies that in conditions associated with cognitive impairment such as dementia in adults,*[32] *the primary channel through which reduced cognition affects HRQoL is through its influence on daily living functionality, i.e. the lost capacity to perform tasks necessary to live and care for oneself independently.*[32-34] *It may therefore be the case that the patient's perception of their own quality of life would not be affected additively by both the loss of communication, skills, and independence due to gross motor dysfunction, and then again by*	This should be deleted.	There are a number of inaccuracies in this paragraph. First of all the company did not assume that the relationship between cognitive dysfunction and motor dysfunction is wholly additive, rather the company position is that there is a partial ***but NOT complete*** overlap on quality of life. Secondly, whilst the impact of cognitive dysfunction on quality of life may be partly mediated through some of the domains in the EQ-5D (e.g. undertake daily activities or anxiety /depression), there are other drivers of quality of life not captured by the EQ-5D. Several studies has shown that key independent drivers of quality of life in patients with cognitive impairment includes perception of autonomy, social participation and intimacy which are not captured in the EQ-5D-5L (Geraerds et al 2019 and 2020 [7,8], Graff et al 2020[10]). The study by Graff et al, showed that the addition of a cognitive function bolt on tool to the EQ-5D-5L was better able to capture the	Not a factual inaccuracy. The application of utility decrements that are constant irrespective of motor function implies an additive effect. The company's assertion is therefore incorrect. The focus of this section is upon EQ-5D, as NICE's preferred means of valuing HRQoL. Evidence that EQ-5D does not adequately capture key aspects of HRQoL relevant to MLD should have been presented by the company in their submission, in support of the use of non-reference case methods. The ERG has revised the text to acknowledge that EQ-5D may not adequately capture the effects of cognitive impairment: *"the primary channel through which reduced cognition affects HRQoL (as measured by EQ-5D)*

cognitive impairment"		impact of cognitive impairments in Stroke patients compared to the EQ-5D-5L alone. This clearly shows that the impacts of cognitive impairment QoL are not adequately captured by the EQ-5D alone. Thirdly, the statement "the primary channel through which reduced cognition affects HRQoL is through its influence on daily living functionality …" misrepresents the findings of the papers referenced. 2 of the 3 papers cited limited their assessment to the domains in EQ-5D. They did not explore domains not captured outside EQ-5D. While the 3rd paper cited indicated resilience coping (not captured by EQ-5D-5L) as a key driver of quality of life in patients with cognitive dysfunction.	*is through its influence on daily living functionality"* *"However, there is evidence to suggest that EQ-5D alone may not adequately capture the effects of cognitive impairment upon HRQoL."*
Page 128 "*In other areas, patients with severe cognitive impairment and complete loss of motor function are considered for modelling purposes as having a 'near-death' quality of life, with a utility of 0.08 – 0.11 for those in a 'persistent vegetative state'*.[36, 37]"	This should be deleted.	As mentioned in the response to the clarification questions, the values cited are not consistent with the NICE reference case because the methodologies in these studies restricted utilities to the possible range of 1 to 0 – i.e. they did not allow for states worse than dead. As such making this direct comparison without the additional context is misleading and inaccurate.	The ERG has edited the text to make it clear these values are bounded at zero. Text revised to add the following: *"(though the ERG acknowledges that these utilities were bounded at zero)."*
On page 129, "*The ERG further*	This should be deleted or revised.	There are several countries which have	The ERG has revised the text to

notes that the UK value set is unique in the use of such negative utilities,[39] *with all other countries having higher minimum values and far fewer health states described as worse than death*." This is factually inacurrate and a misprereentation of the paper by Devlin.		lower or comparable minimum values. For example Denmark and Spain have lower values of -0.624 and -0.654, whilst France value (-0.530) is similar https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/	indicate that the ERG was referring to the EQ-5D-3L value sets. Amend text to *"the UK EQ-5D-3L value set…"*
On page 129, it states "*The sample appeared to mainly comprise caregivers of patients with more advanced disease, as 95% of patients were reported as being unable to walk*." This is factually inaccurate as patients are unable to walk from GMFC 3.	This should be deleted or revised.	It is factually inaccurate to state the caregiver survey comprised patients with more advanced disease – it did in fact cover a breadth of MLD health states. Being unable to walk does not indicate advanced stages of disease. Patients from GMFC 3 are unable to walk but would have a reasonable quality of life if they retain cognitive function (utility value = 0.38)	Not a factual inaccuracy. The reference to advanced disease is qualified with the word "more". It is therefore is clear that the ERG is not referring only to advanced disease. The point is otherwise valid as 5% of the patients reflect 3 of the 7 health states.

Issue 4 Misalignment of company submission with scope (HSCT and MLD -21 exclusion from eligible population)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, top row of table. The report states: *" In the ES-EJ sub-population a patient is excluded even though they received treatment and would be otherwise eligible under the marketing*	Please delete paragraph.	The EMA accepted this type of patient would be ineligible hence the rationale of including the requirement for "physicians to check that the patient hadn't declined and is still clinically appropriate" in the SmPC. As mentioned in the company submission	Not a factual inaccuracy. No revision made. Given the information available, the ERG stands by its interpretation of the SmPC recommendation with regards to this patient, as set out on page 51

authorisation. This exclusion leads to the proportion of stable partial responders being overestimated." This is factually inaccurate as this patient would not be eligible as per the terms of the label.		this rationale was informed by analysis of treatment failures to identify baseline predictors of treatment benefit. MLD 21 had an IQ = 87 and GMFC 1 at baseline and experienced a **decline** in gait (walking ability) between screening and baseline (prior to conditioning). Moreover the SmPC clearly warns that patients should not have the drug if they have clinically deteriorated as this would indicate they may be entering the rapid progressive phase. Furthermore, the company sought the opinion of UK clinicans regarding this patient to ascertain whether they would be treated in real clinical practice. The information received states that clincians would not treat because the SmPC states not to, and transplanters would also not take this risk especially for patients who were already very close to the cut-offs specified for treatment (IQ ≥ 85 and GMFC ≤ 1). The experts at the specialist centres state that they are experienced in such scenarios in neurometabolic conditions and regularly have to decline treatment due to progression between screening and	of the ERG report. The ERG notes that page 182 of the Clinical Efficacy report provided by the company states, about this patient:  (emphasis added) i.e., rapid progression appears to have occurred AFTER treatment, not before. Removing patients such as this from eligibility appears to be a post-hoc decision, made at least partly because of that patient's rapid deterioration after treatment, and excluding them could lead to a biased interpretation of the data. It effectively ensures that there is no possibility of treatment failure, which the ERG considers an unrealistic proposition. More broadly, the ERG also

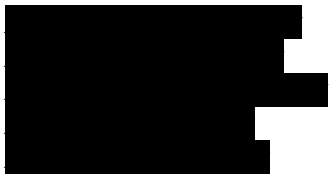
		treatment. They also state that when consenting families at screening they are made aware that if progression occurs which makes their child ineligible they will not treat. The phrase "do no harm" was stated..	considers that this highlights an important issue: accepting that *some* level of pre-treatment progression would be expected in ES-EJ patients, how should the SmPC guidance be interpreted regarding the pre-treatment identification of EJ-ES patients who have entered rapid progression. i.e. what constitutes rapid disease progression? The ERG also notes evidence showing that if rapid disease progression was suspected, then patients were excluded from the study before receiving treatment: [redacted] (see Table 7 footnote, p66 of Summary of clinical efficacy document). This raises the question: if patient [redacted] really had rapid progression before treatment (as stated by the company) why were they not also withdrawn by the investigator?

Page 18 table 1 row 2. The report states: " *The ERG notes that the company's economics advisory board provided testimony that indicated HSCT was used in some patients*."	Please amend to: "not routinely used in these patients"	This is an inaccurate representation of the advisory board conclusion which was that: "Overall, experts indicated that HSCT would not be routinely used even in a world without gene therapy, therefore making it an inappropriate comparator for OTL-200" - see page 1 of the advisory board minutes and page 4 of the report.	Not a factual inaccuracy. No revision made. The ERG also notes that the questioning on HSCT to the advisory board was lacking applicability to the population specified in the NICE scope. i.e. the experts were not asked about the use of HSCT specifically in pre-symptomatic or early symptomatic patients. This limitation in the applicability of the questioning on HSCT means the survey results may underestimate HSCT use (see p43 ERG report).
Page 18 table 1 row 2. The report states: "*Further advice from the ERG's own clinical advisor confirmed the use of HSCT and suggested that there would be significant overlap between the patient group eligible for HSCT and those eligible for OTL-200*." It is inaccurate to state that there is significant overlap as there is clear evidence to indicate that it	Please delete.	LI and EJ patients account for over 80% of the eligible patient group for OTL-200, for which there is clear evidence that HSCT is not used. For the 20% of patients who may be eligible for HSCT, there is a high risk of graft vs host disease (GvHD) in MLD patients. Secondly, Orchard maintains that HSCT it is not used routinely in clinical practice. As routine use in clinical practice is the definition of a comparator in the NICE reference case, it is not appropriate to use HSCT as a comparator in this case. As previously stated on the use of HSCT, experts at the	Not a factual inaccuracy. The ERG is reporting clinical opinion provided. For clarity we have amended *"significant overlap" to "some overlap"*.

would not be used in LI patients and ES-EJ patients.		SEE noted that HSCT would be used in rare instances and only for late onset (i.e. LJ and adult) PS patients; HSCT would generally not be considered an option for early onset (i.e. LI and EJ) and symptomatic patients. Finally, decisions regarding the use of HSCT where it has not been specifically indicated (MLD) are made by a national multi-discipliniary team involving experts across the country who discuss the use of HSCT in metabolic conditions. The clinical expert Orchard sought advice from regarding this matter stated that in the 15 years has been a member of this MDT, *no* LI or early juvenile MLD patient has been given HSCT even though some clinicians may have considered it and sought advice on the matter.	
Page 18 table 1 row 4. The report states: "*...evidence on the HSCT is limited, but suggests that in the right patients HSCT is effective at delaying progression of disease and prolonging survival*."		This is an inaccurate and incomplete statement as there is also evidence to indicate that the use of HSCT in MLD patients has been shown to accelerate disease progression compared to best supportive care (Beschel et al 2020). The wealth of evidence all points to inconsistent outcomes with HSCT in early onset MLD patients.	Not a factual inaccuracy. No revision made.

Page 18 table 1 row 4. The report states: " *This will reduce the comparative effectiveness of OTL-200*. " It is inaccurate and highly speculative to say that including HSCT as a comparator would reduce the ICER of OTL-200.	Please delete this sentence.	HSCT has been associated with safety issues (including but not limited to; risk of mortality, Graft versus Host Disease and future graft failure due to immune rejection, in addition to side effects of being on immune suppressants) as well as the fact that in some cases it has been shown to accelerate disease progression (Beschel et al 2020). Furthermore, the ERG themselves refer to HSCT as only a potentially palliative treatment only in MLD patients. Based on this, without HE modelling it is premature and possibly inaccurate to state definitely that HSCT woud reduce the comparative effectiveness of OTL-200.	Not a factual inaccuracy. No revision made. This statement is made based on the results in Table 11 of the ERG report which clearly indicates that in some patients HSCT can stabilize the course of the disease for many years.
On page 94, "*Patients included in the post hoc subgroup of the integrated analysis included 24 patients covered by the marketing authorisation, excluding data from the 3 patients who would not be covered by the marketing authorisation for OTL-200 and a further patient who progressed shortly after treatment, but who would be covered by the marketing authorisation*." This is not accurate nor a reflection of the licensed indication for OTL-	Please reword sentence as factual inaccuracy.	The integrated analysis presented in the submission included 25 patients covered by the marketing authorisation, and excludes data from the 4 subjects who do not fulfil the eligibility criteria for OTL-200.	Not a factual inaccuracy. No revision made. See first response to Issue 4

200.			
On page 99, the ERG states "…*that there would be significant overlap between the patient group eligible for HSCT and those eligible for OTL-200*" There isn't a significant overlap between potential patient populations.	Suggest deleting or removing the word significant and replace with "there would be a very small potential overlap *between the patient group eligible for HSCT and those eligible for OTL-200*"	As already mentioned in response to a similar factual inaccuracy on page 18. This seems to misrepresent the clinical feedback received by the ERG which suggested only presymptomatic EJ patients (representing 17.5% of the eligible population) may be eligible for HSCT. This does not represent a significant overlap. And as previously stated, clinical opinion from a MDT country wide team does not consider HSCT to be a viable option in LI or EJ MLD patients either.	We have changed *"significant overlap"* to *"some overlap"*
On Page 41 the report states: "*The CS stated that... the use of allogeneic HSCT has been limited to patients with late-onset variants (i.e. late-juvenile and adult patients), given the slower rate of disease progression in the early stages and the lack of treatment alternatives*."	Please update to "The CS stated that... the use of allogeneic HSCT has been limited to patients with late-onset variants (i.e. late-juvenile and adult patients), given the slower rate of disease progression in the early stages, the lack of treatment alternatives *and potential complications associated with HSCT* ."	This is misleading as Orchard also highlighted the safety concerns see Pg 76 of the company submission.	Not a factual inaccuracy. No revision made.
Page 41 the report states: "*The ERG's clinical adviser added that if there were a choice between allogeneic HSCT and gene therapy, gene therapy would be preferred. OTL-200 should therefore be viewed as a*	Please delete the phrase "OTL-200 should therefore be viewed as a replacement for allogeneic HSCT in the treatment pathway".	As previously stated, Orchard and clinical experts do not consider HSCT to be a comparator that is routinely used in clinical practice, and it is certainly not a replacement as it will be 1st line in eligible patients whereas HSCT is not.	Not a factual inaccuracy. No revision made. The ERG is reporting clinical opinion.

replacement for allogeneic HSCT in the treatment pathway."			
On Page 78, the report states: "*Of the nine patients with GMFC-MLD level 0 at baseline four appear to show a clear benefit, four follow a decline similar to natural history and one died as a result of HSCT treatment."*	Please reword to "*Of the nine patients with GMFC-MLD level 0 at baseline four appear to show a clear benefit, four follow a decline similar to natural history and one died as a result of HSCT treatment.However several of the patients who had benefit had complications such as acute graft versus host disease "*	This paper's supplementary information also reports Graft versus host disease complications, which have been excluded here but are very relevant and contribute as to why HSCT is not a valid comparator.	Not a factual inaccuracy. No revision made. The cited text relates to a table of GMFC-MLD outcomes.
Page 51, The report states: "*The company supplied no data to justify the claim of "rapid progression" before cellular harvest and treatment for this patient* [MLD 21]." It is factually inaccurate to say that the company did not provide evidence of rapid progression.	Please delete the sentence entirely	During ERG clarification questions, the company provided the Summary of Clinical Efficacy report and on page 182, it states that the patient had a progressive worsening of the gait between screening and baseline (conditioning), which backs up the company assertion that the patient had rapid progression when put into the context that decline in early symptomatic patient is normally slow. This assertion was echoed by a UK clinical expert who reviewed this case, and confirmed that they would not treat this patient with Libmeldy, as they would be outside of the SmPC indication. Moreover the EMA accepted this patient was a treatment failure as reflected in the EPAR, which is why there is such specific wording in the SmPC to including that precaution and	Not a factual inaccuracy. No revision made. No numerical quantification of the "progressive worsening" (such as change in GMFM total score) was provided to give context for the change i.e. enabling comparisons with pre-treatment changes in other ES-EJ patients Page 182 of the clinical efficacy report provided states: 

		so avoid these patients being treated in post-approval settings.	[redacted] The ERG reiterates that this quite explicitly indicates that this patient may have entered the rapid disease progression phase AFTER receiving treatment. The ERG considers that the patient was still eligible for treatment with OTL-200 at the baseline assessment.
Page 51, the report states: "*The SmPC also states (when discussing treatment failures) that of the three early-symptomatic EJ patients who showed deterioration in both motor and cognitive functions comparable to that observed in untreated patients "two out of the three patients showed deterioration between screening and baseline (onset of conditioning regimen) assessments*". The implication being that one deteriorated after treatment. ", which is factually inaccurate.	Please delete this sentence or rephrase accordingly	This is a factual inaccuracy and the wrong inference as it seems to imply that MLD21 was the patient who did not see a decline between treatment and baseline. it is clearly stated on page 182 of the summary of clinical efficacy that MLD04 and MLD21 were the two ES-EJ patients who had deterioration between screening and baseline as shown by the respective statements "MLD04 was an early-symptomatic EJ subject treated **following rapid disease progression between Screening and treatment.**" and "Subject MLD21 was an early-symptomatic EJ MLD subject diagnosed at just under 6 years of age. The subject achieved normal motor milestones. At 5 years of age, the subject had motor difficulties	Not a factual inaccuracy. No revision made. See response immediately above and the first Issue 4 response.

		manifesting as difficulty running or climbing stairs. Language difficulties presented as slurred and sluggish speech and difficulty writing, both in holding the pencil and in recalling which letters to write. **The subject's gait progressively worsened between Screening and Baseline.**"	

Issue 5 Re-classification of patient responders

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 table 2 row 3 the report states: " *Patients who have experienced a decline in GMFC score more than 12 months after treatment should be classified as unstable*. "	Please amend paragraph in line with the evidence.	Orchard disagrees with this approach for two main reasons: Firstly, some of the LI patients (e.g. MLD06 see Figure 1.1.41 included in Appendix A submitted in the response to clarification questions) who declined within a few months after 12 months, have remained stable for 3 years after that decline thus indicating likely stabilisation. To infer these patients would continue to decline goes against the observed evidence. Secondly, the ERG seems to have also classified as unstable partial responders, patients who had a temporal worsening of their GMFC score that subsequently reversed back (e.g. MLD14 appears to be classified as an unstable partial responder by the ERG despite reverting back to	Not a factual inaccuracy. The ERG appreciates the company may have specific concerns with the ERG approach, but the position put forward represents our considered opinion of how best to classify the patients given the stated mode of action and the limited evidence available.

		GMFC 2 after a temporal drop to GMFC 3).	
On page 94, "*The ERG is also unclear on the rationale for the updated assumptions which revise the distribution of GMFC states patients stabilise….This may not be reasonable given the very limited follow in several patients ([redacted] patient had less than 12 months follow up*)" This is factually inaccurate.	Delete sentence.	All patients had 12 months+ follow-up see table 1.1.46 of appendix A supplied with clarification questions response. The ERG seems to confuse having < 12 months of GMFC measurements with the follow-up period. As mentioned in the company response to the clarification question, as GMFC is validated for use in patients 18 months and older, some of the LI patients had their first GMFC measurement several months after treatment. As such the follow-up post 1st GMFC measurement does not equate to the total follow-up for that patient.	The table referred to on page 683 of Appendix A appears to indicate that 1 patient did not have 12 months follow up. The ERG has however, updated to reflect the fact that some patients did not have 12 months follows post initial GMFC assessment. Text amended to: "*This may not be reasonable given the very limited follow in several patients ([redacted] patient had less than 12 months follow up after initial GMFC assessment)"*
On page 105, "*It is unclear then why [redacted] of patients with the slower progressing EJ variant would be expected to experience continued decline compared to [redacted] in LI, when the natural history of these variants may indicate otherwise.*" Percentage of pateints continue to decline in LI group is 7.2%.	Please amend to 7.2%.	The proportion of patients progressing is based entirely on the data from the trials, and will be affected by the small n numbers. However, Orchard felt it would be more appropriate to use the evidenced trial data rather than clinical opinion to inform this parameter. In the LI group (n=9), 40% were full responders, of which 88% of the remaining 60% stabilised at either GMFC 1 or 2 leaving 7.2% that progressed. In the PS EJ group, 60% of the	Amended as suggested.

		population were full responders leaving 40% who were classed as partial reponders (n=2) - one of which stabilised, and the other that progressed, hence the 20% value.	
On page 107 the ERG state, "*Examples of a pattern of apparent stability followed by a decline in GMFC-MLD stage can be seen across the three modelled disease variants.*"	Please delete this sentence	This is factually inaccurate as no decline was seen in any patient marked as full responder. Furthermore, the patient profiles for trajectories presented in Figure 14 in the ERG report aren't complete, and omit graphs where it is much clearer to see that the patient has stabilised, which is potentially misleading for the Committee.	Not a factual inaccuracy. The ERG has revised to clarify it was is referring to stablilised partial responders Text amended to "*a decline in GMFC-MLD stage can be seen in several stabilised partial responders across the three modelled disease variants*"
On page 157, Table 32 of the report the updated response proportions are incorrect.	Update the table accordingly	Whilst the company acknowledges the ERG's rationale for excluding patients with insufficient follow-up, the ERG does not seem to have done that correctly. For example, the presymptomatic EJ patient who died due to cerebral infarction should have also been excluded due to insufficient follow-up and not classified as an unstable partial responder (as this patient has no evidence of disease progression before death). In addition, as mentioned in Issue 4, MLD21 would not be eligible for treatment as per the SmPC, as such should not be	Not a factual inaccuracy. No revisions made. The death of patient is not the same as lack of follow up and therefore the ERG does not consider this to be inconsistent application of the decision rule. In classifying the patients, the ERG came to the judgement that the death of patient is indicative of treatment failure. In this respect the ERG notes that the company

		included in the classification of responders. Hence the proportion of partial stabilised responders and unstable partial responders should be updated accordingly. .	appear to have come to a similar conclusion as they also classified this patient as an unstable partial responder. As stated above, the ERG does not agree that patient MLD21 would be ineligible for treatment.

Issue 6 Errors in the ERG's corrections to the company base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 117 and Page 153, the ERG report identified two issues in how the company modelled mortality in its updated model. The first issue: *implementation of the parametric curve for GMFC 6 mortality by the company was wrong and leads to the model significantly overestimating survival time*. The second issue: *concerns the choice to implement separate survival models for LI and EJ patient*s. The interpretation of the company's	Revert to the company's approach to modelling MD-related mortality	Firstly, it is factually inaccurate for the ERG to state that the methodology for estimated MLD-related mortality implemented in the revised company submission was wrong and overestimates survival. The probability of death used in the revised company submission was based on age, such that in the survival function *S(t),* t represents age (i.e. time from birth). For clarity, this survival estimate from birth was not appended onto/added to patients after entering GMFC 6. When a patient reaches GMFC 6, MLD related mortality is applied based on the patient's age at that cycle. This is also the method that is used to apply all-cause mortality (based on general population)	The company are correct in so far as the ERG corrections does not fully address the error in the company model. The company approach, however, is not correct. Survival from birth cannot be used to model survival because OTL-200 impacts on survival. An appropriate mortality hazard cannot therefore be derived from survival in patients receiving BSC. This also cannot be derived from the

approach by the ERG is incorrect. Furthermore, in analysing the ERG's corrections to the model, Orchard has identified errors in the corrections actually made by the ERG		based on the patient's age for GMFC 6. This method to estimate time-dependent survival in GMFC 6 was implemented in response to feedback from the ERG clarification stage to incorporate a function without constant hazards. The approach by ERG in its corrections is incorrect for the following reasons: 1. The ERG is extrapolating and fitting parametric curves based on K-M data where survival, in the survival function *S(t),* t represents the time after entering GMFC 6. However, the formulas in the model are still using age as the dependent variable (i.e. t still represents age). This leads to a substantial deviation from the clinical trial data (presented in Figure 1 at the end of this document) 2. Further, this creates a clinically implausible situation where age in the model is equivalent to the time after entering GMFC 6. This would assume that patients enter GMFC 6 at birth, which is clinically implausible. o For example, in the ERG model a patient entering GMFC 6 at 51 months would have a mortality applied that is consistent with a patient that had already spent 51	data on survival in OTL-200 patients due to the short follow up. The ERG's approach is appropriate in so far as it uses the correct survival data (survival time after entering GMFC 6), but is not implemented in the model correctly. The ERG has implemented a second correction that reconfigures the model calculations adding memory to the Markov model. All model results have been updated accordingly. The ERG also highlights that the company's PFC response did not include any description of how the survival analysis had been implemented in the economic model, specifically excluding any mention of the fact that their approach relied on age to determine the survival

		months in GMFC 6. 3. This leads the ERG proposal to substantially overestimate mortality in GMFC 6 and deviate largely from the Orchard Therapeutics TIGET Natural History Study data (see Figure 1). 4. To amend the model formulas to implement the ERG approach, the duration of time each patient has spent in GMFC 6 following their entry into GMFC 6 would need to be known. 5. However, the memory-less nature of the Markov model structure prevents the model from capturing the duration of time patients have spent in GMFC 6. This is further prevented by patients not entering GMFC 6 at the same time. The ERG method was considered while the model was being updated during the clarification stages, however the issues above meant that this approach could not be used.	probability. This was less than helpful and relied on the ERG to interrogate the economic model to ascertain what had been done. The ERG requests that the company provide a clear and complete explanation of all model changes to avoid such issues in the future.
On Page 153, the ERG state the updated model has as an error "*the proportion of stabilised partial responders assumed to remain GMFC 0, which led the model to overestimate progression of these patient*." This is factually incorrect as the model doesn't assume partial responders stabilise at GMFC 0.	Suggest this sentence is rephrased to better illustrate the correction made by the ERG	The model did not assume any partial responder stabilised at GMFC 0. Only full responders were assumed to stabilise at GMFC 0.	The ERG has corrected this typo. New text reads as follows "*the proportion of stabilised partial responders assumed to remain GMFC 1...*"

Scenarios 4a – 4d on Page 164 of the ERG report contains errors in the results.	Please make the corrections and update the results of scenarios 4a – 4d	Whilst we understand these are exploratory scenarios by the ERG, it appears the duration of effect for full-responders have been inaccurately applied. For example in scenario 4a, the ERG corrected model seems to assume that full-responders would stabilize for only 1 month and partial responders would stabilize for 100 years on average. This error seems to be repeated in each of the other scenarios (b – d) We assume this is an error, as the ERG have not provided a rationale for why the permanence of treatment would differ for full- and partial responders who stabilise.	Not a factual inaccuracy. No revision made. The ERG has revisited these scenarios and has been unable to identify any error. These scenarios treat full and stabilised partial responders largely the same using input value located on the "ERG Data" sheet.

Issue 7 Efficacy of the cryo-formulation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 table 1 row 2 the report states: "*It is therefore currently unclear whether the cryopreserved formulation will achieve the same treatment effects as the fresh formulation*."	Please delete this statement	The counter to this is also valid, that this is as effective as the fresh formulation, especially when coupled with the clinical assessment of the OSR team.	Not a factual inaccuracy. No revision made.
Page 21 table 1 row 2 the report states: "*The ERG identified that some of the*	Please delete the sentence	This isn't factually accurate as the results were within the range reported for the fresh formulation and between 6 and	Not a factual inaccuracy. No revision made.

patients receiving the cryopreserved formulation had stable or declining ARSA activity in the CSF after 6 months, in contrast to improving ARSA activity over that period in patients receiving the fresh formulation."		12months, there was no evidence of decline.	

Issue 8 Adverse events associated with myeloablative conditioning and neuro-disability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 table 2 row 2. The report states: "*Trial evidence suggests some aspects of MLD pathology are treated sub-optimally by OTL-200, with patients continuing to suffer renal tubular acidosis, metabolic acidosis, and hepatobiliary disorders*." It is factually inaccurate to attribute acidosis to MLD and it is also inaccurate to suggest that they are due to progression of MLD.	Please delete this sentence.	Acidosis is due to the myeloablative conditioning and shown to occur in short term, not to the progression of MLD. Clinical opinion confirms that the occurrence of metabolic acidosis and renal tubular acidosis is not an indication of disease progression in MLD. Rather it is an acute condition that is most likely secondary to the myeloablative conditioning or a temporal illness in the patient. Given the clinical trial results show that most of the cases occurred in the pre-treatment or immediately after treatment, it is likely attributable to	Not a factual inaccuracy. No revision made. This is not supported by clinical judgment made by the EMA regarding acidosis. The EMA suggests that acidosis occurs due to MLD related sulfatide accumulation in the renal tubules. The EPAR states: "There were 8 cases of renal tubular acidosis in the pre-treatment phase…the applicant's interpretation [was] that these events are likely to be due to the underlying arylsulfatase deficiency" The pre-treatment phase is defined as

		busulfan conditioning. Moreover there is evidence that has shown acidosis to be a side effect associated with myeloablative conditioning and can be simply and effectively managed without significant impact on quality of life or prognosis of the patient. The company acknowledges that hepatobiliary abnormalities may be due to MLD pathology, but disagrees with the assertion that it indicates disease progression. There is no evidence to suggest that rate of occurrence increases as disease progresses. Moreover it can be easily treated through cholecystectomy without long term implications on quality of life.	prior to the first day of the conditioning regimen. It is therefore implausible that events experienced in this period are attributable to busulfan conditioning. Metabolic acidosis was reported in 3 subjects in the pre-treatment phase, 4 subjects during the treatment phase, 1 subject in the short-term phase, and 1 subject in the long-term phase. The company considered these events to be related to MLD. This does not support the company's assertion that metabolic acidosis is a short-term side effect of conditioning.
Page 21 table 2 row 2 the report states: "*Importantly, the modelled outcomes do not capture the potential effects of continuing peripheral neuropathy observed in the trial.* " And: On page 92, it states: "…*One example of this is progressive peripheral neuropathy, which as*	Please rephrase the sentence accordingly	The ERG fails to highlight that all the patients had peripheral neuropathy at the time of treatment which may suggest why it continued to progress but is trending towards stabilisation. In fact Figure 5 in the ERG report clearly shows stabilisation of NCV score 2 years after treatment. As such it is factually inaccurate to state or suggest that peripheral neuropathy would	Not a factual inaccuracy. No revision made. The ERG's interpretation of an apparent progression of peripheral neuropathy in the trial evidence was shaped by clinical opinion. A description of the '**potential effects** of continuing peripheral

*outlined in Section **Error! Reference source not found.** was noted in many patients receiving OTL-200.*" It is factually inaccurate to assume that progressive peripheral neuropathy is indicative of progressive disease in patients receiving OTL-200.		continue to worsen and lead to worsening of GMFC. Investigators in the OTL-200 trial noted that the NCV scores seen in treated patients were not clinically significant and seemed to have stabilised after 2 years, and would not translate to a loss of mobility or worsening of GMFC score in the future. Furthermore, data from Sessa et al[1] show that overtime remyelination may occur in the PNS following gene therapy, thus indicating a possible reversal of the worsening of peripheral neuropathy overtime. This is supported by the improving NCV values over time in a number of full responders in the early juvenile group receiving OTL-200.	neuropathy observed in the trial' is not a definitive statement of future effects. It is the role of the ERG to highlight issues in the effectiveness data which contribute to decision uncertainty. The ERG does not consider Figure 5 a clear demonstration of a trend towards stability. In the ERG Report, it was concluded that: [redacted] This is not a factual inaccuracy, but an interpretation of clinical data informed by expert advice.

Issue 9 Durability of effect in stabilisers

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12, table row 3 the report states: "*Whilst medium-term graft stability has been demonstrated in other therapeutics, there are factors*	Please delete.	It is unclear why the ERG says there are factors unique to such technologies that may impact long term durability of effect. The ERG does not justify this claim with evidence and misrepresents the evidence	Not a factual inaccuracy. No revision made. The assumption of permanent

unique to all such technologies which may impact the long-term durability of treatment effects." This statement is speculative and is not supported by any evidence.		which shows durability of effect for ex-vivo gene therapy. For example, patients treated with Strimvelis have seen durability of effect for over 20 years and still counting. The company believes that attributing medium term results from allogeneic HSCT to ex-vivo HSC gene therapies is inappropriate giving the potential for immune rejection over time in allogeneic HSCT especially if not well-matched.	graft stability is speculative, and generates very high decision uncertainty, as seen in the ERG's scenario analyses. A permanent treatment effect has not been accepted without caveat in any NICE appraisal of gene therapies. As described in the ERG report, the therapeutic mechanism of OTL-200 is unique among approved gene therapies. This means there may be other factors influencing long-term treatment effect, as outlined in the EPAR. The 20 year period in which Strimvelis has been used in a small number of patients was the case referred to by 'medium term'. This cannot be considered a definitive demonstration of 100-year stability in 100% of patients for a different technology, as assumed by the company.
On page 92, the ERG states	Please delete	The IPD referred to in the ERG report, which was sourced from the EPAR, shows	Not a factual inaccuracy.

"*Stability in terms of gross motor function (GMFM) total score appeared more ambiguous."* This is factually inaccurate.		that the GMFM score for the proportion of LI patients who stabilised aligns with the proportion of patients who are full responders. The company acknowledges that the IPD shows that some patients had some mild decline in their GMFM scores, however the company did not classify these patients as stabilisers as inferred by the ERG.	No revision made. The ERG's argument is that interpretation of stability becomes more subjective in light of the IPD in the EPAR. Without reference to the specific patients in Figure 13 of the EPAR the company considers to have stabilised, it is not possible to comment on the claim that GMFM demonstrates a full response in [redacted] of LI patients. Full response-level stability over more than two time points could be argued for Patients 2, 3, and 4, which equates to only 30% of the patients in this analysis. It is also hard to argue from these data that a further [redacted] of patients have achieved functional stabilisation. The ERG would welcome more complete GMFM IPD to demonstrate the company's assumptions.

Also on page 92, it states "*Similarly, other surrogate markers of disease including …Lansky play scores, all show some* evidence *of disease progression amongst patients classified as full responders.*" This is factually inaccurate, the Lansky scores do not show any evidence of disease progression in full repsonders.	Please delete the sentence	The summary of clinical efficacy shows that all four full responders (GMFC 0) in the PS LI group and all three in the PS EJ group all had Lansky performance status scores of 100 or 90 at baseline and throughout follow-up, indicating that these subjects have been able to fully engage in physically active play or with minor restriction in physically strenuous activity. There is no evidence of disease progression according to Lansky play scores in full responders.	The ERG cannot confirm the information provided by the company based on the information provided in Appendix. The figures provided in appendix A suggest all pre-symptomatic patients had score of 100 at baseline (not 100 or 90 not as suggested) and that some LI patients experienced a decline in these scores. Based on an analysis of this data it does appear that one patient who was a full-responder experienced a modest decline in Lansky play scores at 4.5 and 5 years. It is, however, very difficult to match follow-up times with reported scores given the limited IPD provided to the ERG. In light of the company's assertion that no full responder experienced a decline in Lansky play scores the ERG has therefore modified this sentence to remove reference to Lansky

			play scores.

Issue 10 ARSA CSF decline in late infantile

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 20, "*The ERG noted a decline in ARSA activity in CSF in Late Infantile patients after 24 months. This may be of concern as OTL-200 treatment is intended to increase and maintain ARSA activity.*" It is misleading for the ERG to infer that ARSA levels in the CSF are a concern for treatment efficacy, based solely on these data, which were not significant, and ignoring the PBMC data and clinical opinion.	Please delete this.	The statement by the ERG is factually inaccurate for the following reasons: (1) CSF values do not reflect the intracellular values, in the same way the plasma levels of ARSA do not reflect what is in PBMC. There is considerable evidence to suggest that cellular levels of enzymes do not always correlate with plasma levels which are often lower; (2) This misalignment is recognised in MLD clinical community, hence why recent clinical trials in MLD are looking into CSF sulfatide levels as a better marker (Dali et al 2020, Molecular Genetics and Metabolism Volume 131, Pages 235-244); (3) The apparent decline can also be explained by the reduced number of patients with data for this time point (4) the only effective biomarker would be to measure brain cell ARSA levels which can only be done by brain biopsies which is unethical to perform in these patients, who still alive and are clinically well. (5) As stated in the company submission, response to clarification questions, all patients had ARSA levels within the normal range and no correlation has been shown between levels of ARSA and clinical outcomes.	Not a factual inaccuracy. The ERG notes that in Section 3.2.4.8 we quote the EPAR report, which stated that low levels of ARSA activity in CSF may be indicative of poorer treatment efficacy.

Executive Summary Section 1.1, page 12 the report states that "*The ERG noted a decline in ARSA activity in CSF in Late Infantile patients after 24 months*"	Text should be updated to state that: "The ERG noted a decline in ARSA activity in CSF in Late Infantile patients between 36 months and the next assessment amongst evaluable subjects at 60 months".	The Executive Summary is incorrect. The decline noted in ARSA activity in CSF in Late Infantile between 24 and 36 months is insignificant. The next assessment for ARSA in CSF was at 60 months where a possible decline was noted based on the subset of subjects remaining evaluable at 60 months. Additionally, it is worth reiterating that the levels seen at 60 months were still within the normal range for healthy children (Martino et al).	Not a factual inaccuracy. No revision made.
Section 3.2.4.8, page 74 of the report states that: "*For ARSA activity in CSF the ERG notes the substantial fall in activity among Late Infantile patients from 24 months onwards*".	Text should be updated to state that: "For ARSA activity in CSF, the ERG notes a decline in activity among Late Infantile patients between 36 months and the next assessment amongst evaluable patients at 60 months".	Consistent with Executive Summary Section 1.1. The "substantial fall" language in Section 3.2.4.8 does not correlate with Figure 11 (Pre-Symp LI, page 75) where a decline was noted based on the subset of subjects remaining evaluable at 60 months.	"*Substantial fall*" has been replaced with "*decline*" for consistency.

Issue 11 General description of modelling approach and scenarios presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 table row 13 of the report states: " *It is not fully clear which data were used to estimate a progression modifier applied to partial responders to OTL-200*."	Please delete the sentence.	This is factually inaccurate as the company made it clear in both the submission and clarification that the progression modifier was estimated by calculating the rate of progression between GMFC 2 and 5 for OTL-200 treated patients and comparing it with that of Natural history patients. Moreover the ERG accurately describes the approach in section 5 of the report showing full understanding.	Not a factual inaccuracy. No revision made. The ERG remains unclear as to which patients contributed to this analysis. The CS and PFC do not present this information, stating only that data was from 7 patients in the OTL-200 integrated analysis.

On page 14 table row 13 the report states: "*The OSR-TIGET natural history cohort used was subject to substantial attrition and it may have been better to consider the rate of transition between GMFC 2 and 6 due to lower levels of attrition.*"	Please delete the sentence	It is factually inaccurate to state it would be better to use transitions between GMFC 2 and 6 instead of GMFC 2 and 5 for a number of reasons: (i) Progression between 2 and 5 has been shown to occur at the same rate for late infantile and juvenile patients (Kehrer et al 2011), progression between GMFC 5 and 6 is not equivalent between disease variants; (ii) progression between GMFC 2 and 5 is linear and represents the progressive phase, while between 2 and 6 it is not linear.	Not a factual inaccuracy. The ERG acknowledges that there may be benefits of using GMFC 5, but as stated there are few observations for GMFC 5. Using GMFC 6 therefore represents a reasonable alternative in the absence of this data. For accuracy the ERG has updated the text to read as follows: *"The OSR-TIGET natural history cohort used contained a substantial number of missing data points and it may have been better to consider the rate of transition between GMFC 2 and 6 due to lower levels of missing data.*"

Page 87 of ERG report states"…*such that a score of 5 indicates complete loss of locomotion and sitting without support, and 6 denotes a state of complete loss of motor function*." There is an incorrect reference to the GMFC classification level.	Please amend to "Such that a score of **4** indicates complete loss of locomotion and sitting without support."	The GMFC-MLD published classification states that for GMFC 5 "No locomotion nor sitting without support, but head control is possible." It doesn't have much of an impact but is factually inaccurate.	Text revised *"...such that a score of 5 indicates near complete loss of locomotion and sitting without support, and 6 denotes a state of complete loss of motor function*." The ERG acknowledges the omission of reference to head support and has edited to add the word "near". The ERG has, however, not included reference to head control so as to retain readability of the sentence. The ERG considers this reasonable given the reference to the full descriptions in the text and the company's repeated use of similar phrasing in the CS.

On page 95, "*Fourthly, the modelled distribution of initial GMFC scores in the LI sub-population is inconsistent with the reported baseline characteristics in the integrated efficacy analysis.*" This is factually inaccurate as there was no inconsistency between the initial GMFC scores in the the LI group compared to the reported baseline characteristics in the integrated efficacy analysis.	Please delete the sentence	The ERG wrongly implies that the first GMFC score were taken always at baseline which was not the case for some patients as they were too young for GMFC tests (minimal age is 18 months). In some cases there was up to 12 months between baseline and first GMFC assessment taken when the patient was 18 months or older. For example, MLD-22 had their first GMFC assessment 12 months after treatment when they were 20.3 months of age. While MLD-HE01 had their first GMFC score 9 months after treatment when they were about 18 months old	The ERG has revised to make it clear that we are referring to initial GMFC score rather baseline characteristics. Text amended as follows: *"Fourthly, the modelled distribution of initial GMFC scores in the LI sub-population is inconsistent with the reported initial GMFC scores observed in the integrated efficacy analysis"*
On page 111, "*The ERG is concerned that the [redacted] patients treated with OTL-200 upon whom the pre-symptomatic multipliers are based include patients not covered by the marketing authorisation….*"	Please delete this sentence	This is a factual inaccuracy and is based on an assumption the ERG has made. Orchard has not included the 4 excluded patients in the analysis, but rather focussed only on the partial responders in the indicated population who showed decline between GMFC 2 -5.	The CS and PFC response do not provide sufficient information to establish whether the 4 patients not covered by the marketing authorisation were included in this analysis. The critique therefore represents a genuine concerns of the ERG. The ERG has, however, removed this statement to avoid misleading the committee and replaced it with text outlining general concerns with identity of these patients.

Also on page 111, "*It is also likely that the majority of patients in the OTL-200 group had the EJ variant, whilst it appears that most patients with an eligible disease course in the TIGET cohort had late infantile disease*" Whilst not potentially inaccurate, Orchard is unclear to the relevance.	Please delete this sentence	Orchard is unclear why this is relevant as the rate of disease progression between GMFC 2 and 5 are the same for LI and EJ (Kehrer et al 2011).	Not a factual inaccuracy. No revision made. The ERG considers it appropriate to identify differences between the cohorts as it is plausible that this may contribute to bias in the estimation of the progression modifier.

Issue 12 Company's response to data requests

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 table row 2 of the report states: "*Limited information on patient baseline and results data were submitted, especially for the untreated cohort*."	Please delete	This is factually inaccurate as Orchard presented the baseline and results for the drug in response to the clarification question (see response to question B1c). Moreover the baseline characteristics were also detailed in Section 3.1.3. of the OTL-200 Summary of Clinical Efficacy document which was shared with the ERG as part of the response to clarification questions. However, Orchard would like to apologise to the ERG as it had fully intended to provide the CSRs as requested and believed they were included in the reference pack sent with the ERG clarification questions.	Not a factual inaccuracy. No revision made. In the absence of IPD the ERG requested very specific baseline data for both OTL-200 and comparator cohorts (see the table at end of the ERG's points for clarification document). This table was not completed by the company though some large documents were supplied. For the OTL-200 cohort *some* baseline data were found in a 1000+ page appendix, but data on important characteristics were missing (e.g. genotype, treatment

		However it appears these documents were not successfully transferred to the ERG.Nevertheless, Orchard believes all the information contained in the individual CSRs are in the OTL-200 Summary of Clinical Efficacy document which was successfully shared with the ERG. In addition the IPD data of all the key outcomes used in the model were also included in the submission.	dose, vector copy number, age at onset). For the comparator cohort there was almost no baseline data and results data were limited in detail. Moreover, the ERG does not consider that supplying incomplete and scattered data across large documents constitutes a reasonable response for specifically requested data.
Page 19 table 1 row 2. The report states:" *the ERG notes that provision of IPD and clinical study reports (both were requested by the ERG) could have resolved some uncertainties in analysing the trial data and evaluating comparisons with untreated patients*."	Please delete the sentence	This is an inaccurate statement as IPD data were presented for the key outcomse used in the model (appendix A submitted as part of the response to the clarification questions) and the Summary of Clinical Efficacy was shared with he ERG. However, as already stated above Orchard apologises for not including the CSRs in the reference pack, it was an error on the company's part.	Not a factual inaccuracy. No revision made. Provision of IPD means providing an analyzable IPD data set. This was not provided. In fact, the company explicitly declined to provide it (Response to clarification A17)

Issue 13 Fulfillment of criteria to apply a discount rate of 1.5%

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 101, the ERG asserts that the case for applying the discount rate of 1.5% has not been sufficiently made because it disagrees with "*the company's assertion that GMFC 1 and GMFC 2 represent near-normal health*." The assertion that GMFC 1 and 2 does not represent near normal health is factually inaccurate especially within the context of several studies which have shown that walking impairments (such as reduced quality) or with some support has marginal impact on patients quality of life.	Please amend accordingly	The assertion that patients in GMFC 1 and 2 with normal cognitive function do not have near full health is inaccurate. Studies such as Shafrin et al 2017 show that walking impairments (such as reduced quality) or with some support has marginal impact on patients quality of life. The study showed a 0.046 change in QOL for every 100m reduction in 6MWT[2]. Considering that the average 6MWT for the general population is between 400m and 700m,[3] independent walking with reduced quality of performance (GMFC MLD 1) or with some support (GMFC-MLD 2) can be considered near-normal health.	Not a factual inaccuracy. No revision made. The application of these criteria is subjective and the ERG is simply stating an opinion that GMFC 1 and 2 do not qualify as near full health. Regarding the new evidence cited. The ERG notes that motor skills are but one element of the GMFC 1 and 2 health state and that other factors may also contribute to reductions in quality of life.

Also on page 101, "*The contention that all patients retain normal cognitive abilities is also demonstrably false as the clinical data made available at the clarification stage show that several patients experience either mild or moderate decline in cognitive function*." This is factually inaccurate as there are no data that show patients in GMFC 1 or 2 had moderate or mild cognitive function.	Please delete this sentence.	There are no data that show OTL-200 treated patients in GMFC 1 or 2 had moderate or mild cognitive function. All these patients had normal cognitive abilities as measured by IQ/DQ.	The text has been revised to make it clear that there is evidence of cognitive decline in some of the patients receiving OTL-200. Text amended as follows: *"The is also broader evidence of cognitive decline in patients treated with OTL-200, it is therefore unclear whether cognitive abilities will be completely retained in patients stabilised in GMFC 1 and 2"*

On page 102, "*All patients in this cohort will definitionally experience some decline in function and because the effects of OTL-200 are limited to the prevention/slowing of decline, all patients in the ES-EJ population with necessarily not been full health*." This statement isn't accurate and is not supported by the evidence.	Please delete this sentence or reword	As written the statement seems to suggest that all ES-EJ subjects would have decline in function post-treatment. This is factually inaccurate as there is no evidence to suggest that and flies against the presented evidence that none of the ES-EJ subjects declined below a GMFC score of 2 within the follow-up period.	The text has been revised to clarify that the ERG was referring to the fact that these patients have already experienced some decline which cannot be reversed. Text amended as follows: *"All patients in this cohort will have definitionally experienced some decline in function, representing the fact they are treated with some symptoms of disease. All patients in the ES-EJ population will therefore necessarily not be in full health."*
Also on 102, "*Durable clinical efficacy has been demonstrated up to 60 months in a small number of patients (n=3), with a maximum follow-up of 77 months, there are no data beyond this*." This isn't factually correct, there are much longer term data and in more patients than the ERG is stating here.	Please amend to: "up to 90 months with 28% of patients (n = 7) having more than 60 months of follow-up data, with maximum follow-up of 90 months".	This is factually inaccurate and should read, "up to 90 months with 28% of patients (n = 7) having more than 60months of follow-up data, with maximum follow-up of 90 months. See Table 1.1.46 of Appendix A which was made available to the ERG This statement also ignores the fact that Strimvelis, a similar ex-vivo gene therapy platform, has demonstrated durable efficacy for over 20 years and still counting.	Not a factual inaccuracy. The text has been revised to make it clear that the ERG was referring to full responders only. Text amended to "*...up to 60 months in a small number of full responders (n=[redacted]) ...*"

Issue 14 EJ MLD patients contributed to nearly half of the trial population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 18, "*OTL-200 has only been fully tested on 35 patients, with very small numbers of patients with the Early Juvenile variant*"	Please delete and amend to correct amount which is actually 19 of 35.	In fact 46% of the trial population had the early juvenile form of the disease in the trial population. (Fresh: LI = 16, PS-EJ = 5, ES-EJ = 8, Cryo (n=6) – LI = 3, PS-EJ = 3)	Text revised to "*with very small numbers of patients for each patient type (LI, PS-EJ, or ES-EJ).*"

Issue 15 Estimation of progression modifier in unstable patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 27 table 2 row 2. The report states: "*In this regard, it may have been better to consider the rate of transition between GMFC 2 and 6*"	Please delete the sentence.	No treatment effect is expected between GMFC 5 and 6.	Not a factual inaccuracy. No revision made. This is a suggestion and helps overcome the limitations of the data where there are few patients with data at GMFC 5.

Page 27 table 2 row 5. The report states: "*Clarity on which patients informed the estimation of the progression modifier is important and will help validate this approach.* "	Please delete the sentence.	This is factually inaccurate as Orchard made it clear that the estimation was based on all partial responders.	Not a factual inaccuracy. No revision made. The company did not make this clear. The PFC response states the data is drawn from the integrated efficacy analysis and that it was based on 7 patients. There are not 7 partial responders.

Issue 16 Gross Motor Function (GMFC-MLD)

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Page 58. The report states: "*The CS provided reported very limited summary data on GMFC-MLD and did not formally compare the results for patients receiving OST-200 to those in the natural history group. The ERG therefore considers analysis of GMFC-MLD using figures presented in the CS; reproduced here*."	Please rephrase this sentence to "*The CS provided reported summary data on GMFC-MLD and formally compared the results for patients receiving OST-200 to those in the natural history group. The ERG therefore considers analysis of GMFC-MLD using figures presented in the CS; reproduced here*."	This is inaccurate, Orchard did provide a formal comparison in the form of panel plots of OTL-200 vs natural history patients and siblings (Figure 1.1.41) as well as a comparison of mean age at entry for each GMFC for OTL-200 vs Natural History groups (Table 1.1.54 and Table 1.1.55). In addition, OST-200 should be OTL-200.	Not a factual inaccuracy. A panel plot of data is not a formal statistical analysis. This typo has been corrected.

Page 58 of the report states: "*Several patients had GMFC-MLD levels of* [redacted] *at baseline, which does not fit with being pre-symptomatic at time of treatment. Most of these patients appear to have been recruited in the compassionate use programme. A possible explanation for this is that these children had delayed onset of walking, so scores were lower, but they had no actual impairment*."	Please rephrase to "*Several patients had GMFC-MLD levels of* [redacted] *at their first GMFC assessment timepoint. Most of these patients appear to have been recruited in the compassionate use programme. A possible explanation for this is that these children had delayed onset of walking, so scores were lower, but they had no actual impairment*."	This is factually inaccurate as no patient had a GMFC-MLD level of 2 or worse at baseline (defined at conditioning). These scores reflect the 1st GMFC measurements taken after treatment and in most of the cases, more than 6 months after treatment which may be as a result of GMFC not being valid for use below age of 18 months.	Amended as suggested.
Page 60, Figure 2. and Figure 3 on Page 62	Replaces this with Figure 1.1.41 of Appendix A provided in response to the clarification questions.	Suggest that the ERG replaces this with Figure 1.1.41 of Appendix A provided in response to the clarification questions, as this shows the treatment baseline	These have not been replaced as the figures in Appendix A do not present the full data set in one figure.
Page 61 table 7 column 2 row 4 "*Stable at Level 1 or 2, number of LI=3*"	Please update to "Stable at Level 1 or 2, number of LI = 4"	Factual inaccuracy should be n=4 (MLD-CUP02 and CUP-01, MLD01 and MLD06) who have spent more than 3 years at GMFC 1 compared to around 15 months at GMFC 0.`	Not a factual inaccuracy. No revision made. This is based on ERG interpretation of stability.
Page 61 table 7 column 4 row 4 "*Stable at Level 1 or 2, number of ES-EJ =1*"	Please update to "Stable at Level 1 or 2, number of EJ = 3"	Factual inaccuracy, this should be 3 patients (MLD8, 14 and 17) who have shown stabilisation for circa of 3 years.	Not a factual inaccuracy. No revision made. As above.

Page 61 table 7 column 2 row 7 "*Possible long-term decline, number of LI =2*"	Please update to "Possible long term decline at a slower rate to NH, number of LI = 1"	Factual inaccuracy, this should be 1.	Not a factual inaccuracy. No revision made. As above. a factual inaccuracy, as above.
Page 61 table 7 column 4 row 8 "*Possible long-term decline limited follow up, number of LI =3"*	Please update to "Possible long term decline at a slower rate to NH, number of LI = 1"	Factual inaccuracy, this should be 1.	Not a factual inaccuracy. No revision made. As above.

Issue 17 Gross Motor Function Measure (GMFM)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 62 of the report states: " *Two show clear decline over time (one was excluded from CS analysis)...*"	Please update to "One patient showed decline over time although at a slower rate compared to NH subjects"	Update to include as patient would be ineligible as discussed earlier in this document.	Not a factual inaccuracy. No revision made. The ERG is simply commenting on the presence of decline not the rate. No clarification of this is necessary.

Issue 18 Survival outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70 of the report states: " *The ERG notes that the CS analysis excludes the* [redacted]	Please delete	Factual misrepresentation of the CS analysis, it should specify that this patient would not be eligible under the licenced indication for OTL-200 as previously mentioned in this document.	Not a factual inaccuracy. No revision made.

Issue 19 MRI total scores

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.4.1, page 58 the report states: "*One possible area of concern is the MRI results in the ES-EJ group. MRI scores were substantially poorer (mean 11.4 after 3 years) than for LI or PS-EJ patients (mean after 3 years: 2.2 and 4.1 respectively), and OTL-200 did not achieve statistically significant superiority to the natural history group for MRI scores in the ES-EJ group*". The wording is incorrect.	The wording should be removed in its entirety.	Comparisons have been made between treated and untreated ES EJ groups. However, the sentence implies age-matched comparisons have been made between disease subtype and symptomatic stage OTL-200 treated patients. Also, contrary to the statement in Section 3.2.4.1, there was a statistically significant difference at 3 years between treated and age-matched natural history patients (treatment difference of 10.9, p=0.013).	Not a factual inaccuracy. No revision made. The ERG is making no implication about age-matching. This is a straightforward interpretation of the primary analysis reported in the CS.

Issue 20 Other inaccuracies

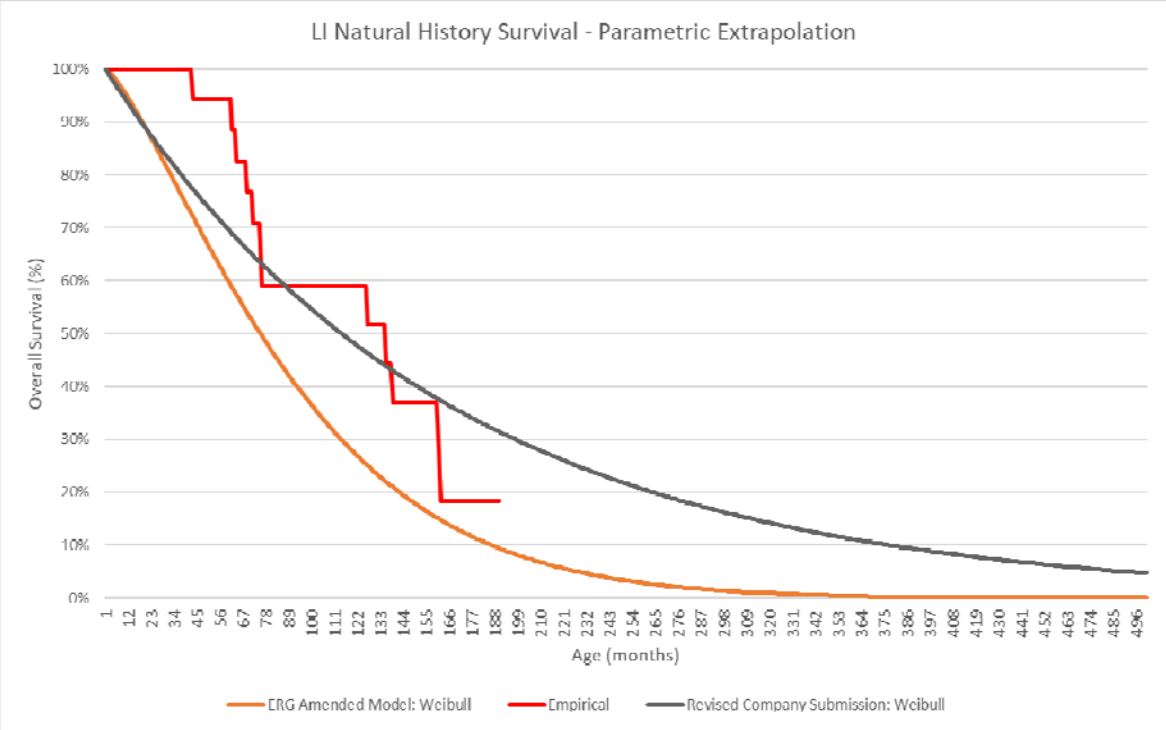
Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive Summary Section 1.1, page 12 the ERG report eport states that "*OTL-200 has been tested in only a few patients, with limited follow-up*". It is factually inaccurate to state that there is only a few patients with limited follow-up, particularly given the ultra-rare nature of the disease and OTL-200's orphan designation.	Text described in description of problem should be removed from the Executive Summary.	The analyses supplied to the ERG are based on data from 35 subjects treated with OTL-200 with a total of 110 years of follow-up post-treatment so far, and the the first patient being treated in 2010. Given the rareity of MLD and the orphan disease designation that OTL-200 has been granted by the EMA, Orchard Therapeutics believes that the description provided is factually incorrect and entirely misleading.	Not a factual inaccuracy. No revision made. This a brief statement of a general issue of small sample sizes. Further, the comment is entirely reasonable; many of the inputs used in the economic analysis are derived from 10 or fewer patients. The ERG would also highlight that the majority of analyses including all the economic analysis is based on 26 or fewer patients not 35 as suggested by the Company.

Table 1: Mean VAS scores for all juvenile MLD health states in each cognition group

Health States	VAS score	SD	95% Confidence Intervals
GMFC0 +moderate cognitive impact	70.52	15.52	57.34 - 66.24
GMFC0 + severe cognitive impact	34.46	25.45	27.30 – 41.61
GMFC1 + normal cognition	77.35	16.51	73.15 – 81.54
GMFC2 + normal cognition	59.85	20.54	53.28 – 66.42
GMFC3 + normal cognition	34.65	20.16	28.92 – 40.38
GMFC4 + normal cognition	18.97	21.14	12.20 – 25.72
GMFC1 +moderate cognitive impact	61.80	17.37	57.34 – 66.24
GMFC2 +moderate cognitive impact	40.76	19.09	35.38 – 46.12
GMFC3 +moderate cognitive impact	26.53	20.91	20.58 – 32.46
GMFC4 +moderate cognitive impact	8.04	16.20	3.48 – 12.60
GMFC5 +moderate cognitive impact	7.75	18.40	3.04 – 12.46

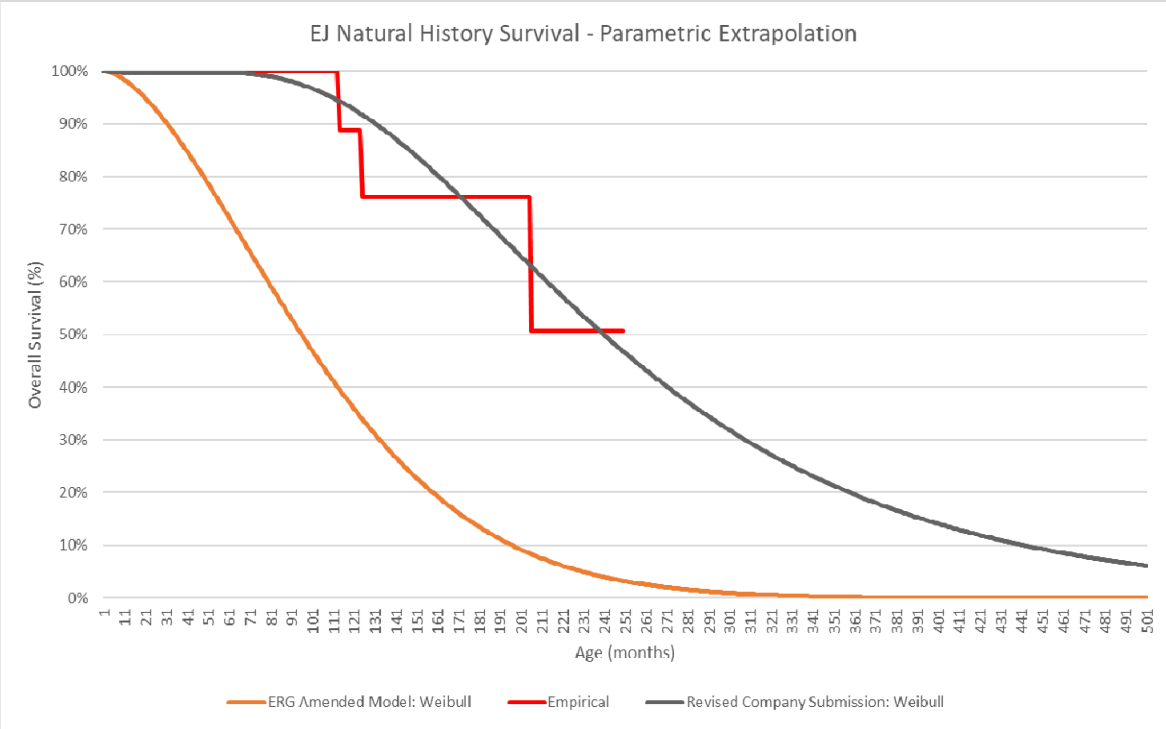
GMFC6 +moderate cognitive impact	-0.69	16.95	-5.45 – 4.07
GMFC1 + severe cognitive impact	28.56	21.93	22.35 – 34.69
GMFC2 + severe cognitive impact	32.89	22.20	27.20 – 38.57
GMFC3 + severe cognitive impact	11.45	18.43	6.27 – 16.63
GMFC4 + severe cognitive impact	4.66	18.36	0.54 – 9.88
GMFC5 + severe cognitive impact	-2.54	17.36	-7.42 – 2.33
GMFC6 + severe cognitive impact	-5.07	16.50	-9.30 - -0.85

Figure 1a. Comparison of ERG-proposed and Company Submission MLD-related Mortality Estimates Applied in the MLD Model for the LI Cohort



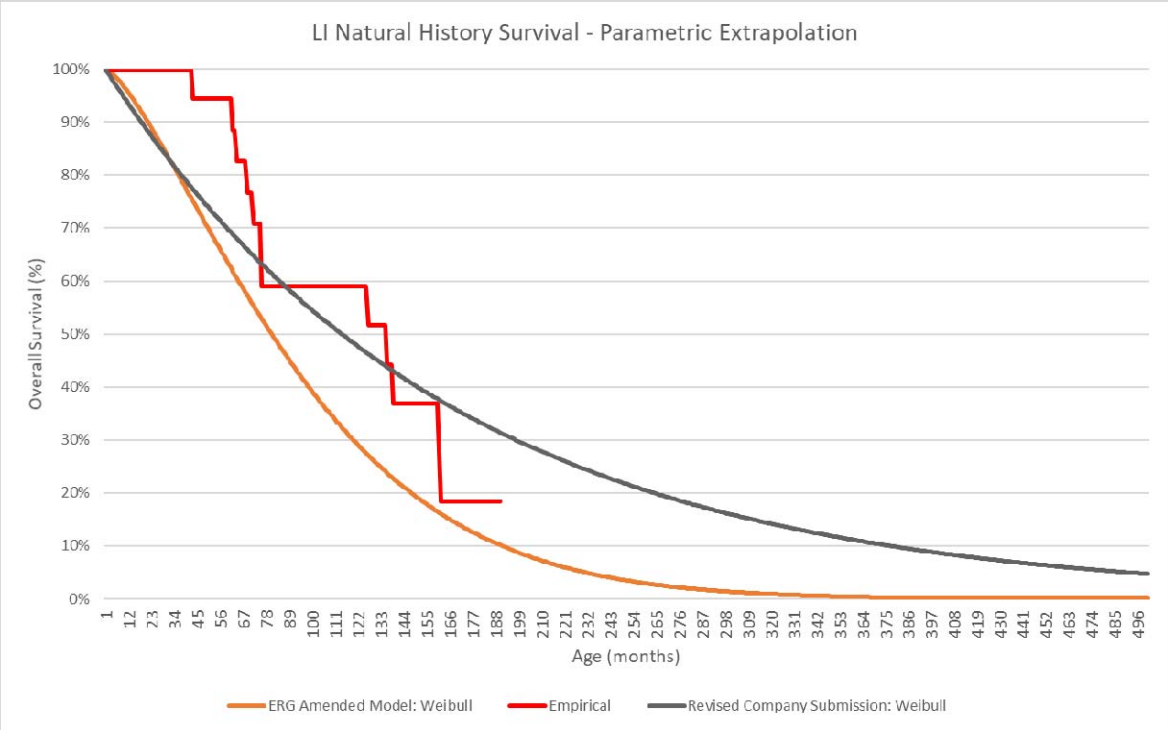
Note: Survival was not amended in the ERG Amended Model, so age 0 months = Age at entry into GMFC 6. Empirical Kaplan-Meier curve represents the survival from birth for LI patients in the Orchard Therapeutics TIGET Natural History Study. The "ERG Amended Model: Weibull" curve is fitted to a Kaplan-Meier curve of LI patients from GMFC 6 to death and underestimates survival in the model. The "Revised Company Submission: Weibull" curve is fitted to the "empirical" Kaplan-Meier curve of LI patients' survival from birth.

Figure 1b. Comparison of ERG-proposed and Company Submission MLD-related Mortality Estimates Applied in the MLD Model for the EJ Cohort



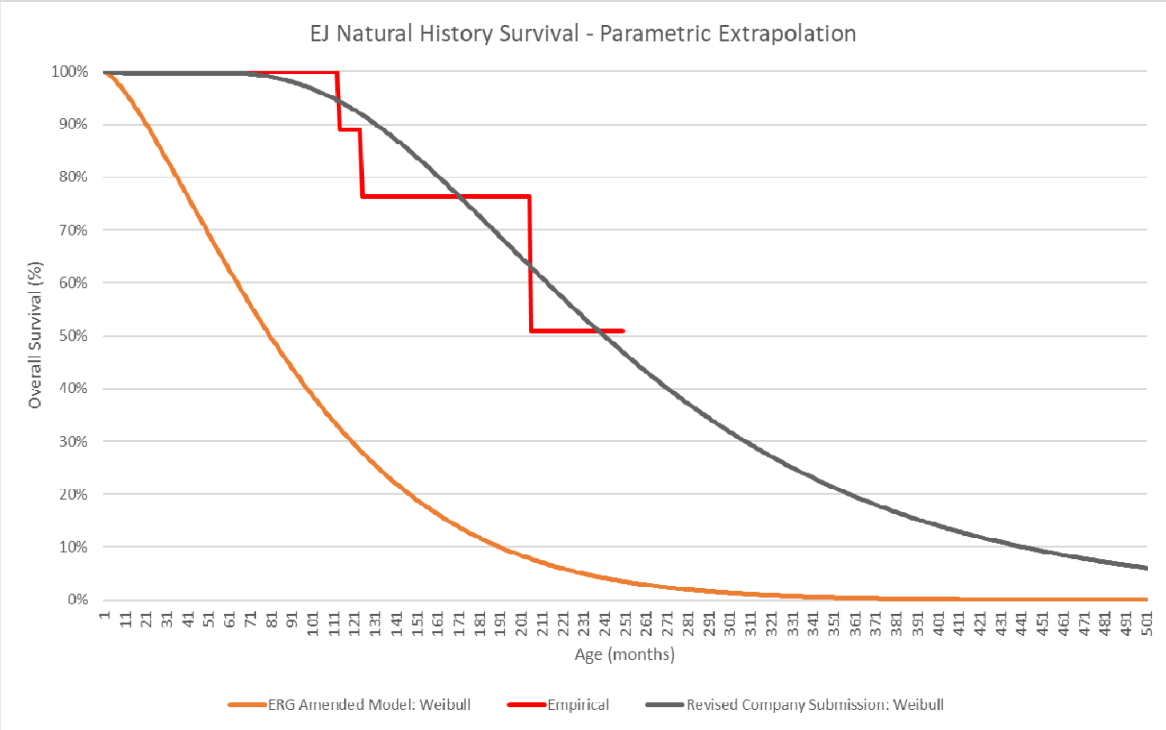
Note: Survival was not amended in the ERG Amended Model, so age 0 months = Age at entry into GMFC 6. In the ERG Amended Model, a PS-EJ patient entering GMFC 6 1 month after model entry (PS-EJ model entry = 45 months) would be applied a mortality estimate of a patient that had already spent 46 months in GMFC 6. Empirical Kaplan-Meier curve represents the survival from birth for EJ patients in the Orchard Therapeutics TIGET Natural History Study. The "ERG Amended Model: Weibull" curve is fitted to a Kaplan-Meier curve of EJ patients from GMFC 6 to death and underestimates survival in the model. The "Revised Company Submission: Weibull" curve is fitted to the "empirical" Kaplan-Meier curve of EJ patients' survival from birth.

Figure 1c. Comparison of ERG-proposed Pooled MLD-related Mortality Estimates (Scenario 9) and Company Submission MLD-related Mortality Estimates Applied in the MLD Model for the LI Cohort



Note: Survival was not amended in the ERG Amended Model, so age 0 months = Age at entry into GMFC 6. In the ERG Amended Model, a PS-LI patient entering GMFC 6 1 month after model entry (PS-LI model entry = 18 months) would be applied a mortality estimate of a patient that had already spent 19 months in GMFC 6. Empirical Kaplan-Meier curve represents the survival from birth for LI patients in the Orchard Therapeutics TIGET Natural History Study. The "ERG Amended Model: Weibull" curve is fitted to a Kaplan-Meier curve of LI patients from GMFC 6 to death and underestimates survival in the model. The "Revised Company Submission: Weibull" curve is fitted to the "empirical" Kaplan-Meier curve of LI patients' survival from birth.

Figure 1d. Comparison of ERG-proposed Pooled MLD-related Mortality Estimates (Scenario 9) and Company Submission MLD-related Mortality Estimates Applied in the MLD Model for the EJ Cohort



Note: Survival was not amended in the ERG Amended Model, so age 0 months = Age at entry into GMFC 6. In the ERG Amended Model, a PS-EJ patient entering GMFC 6 1 month after model entry (PS-EJ model entry = 45 months) would be applied a mortality estimate of a patient that had already spent 46 months in GMFC 6. Empirical Kaplan-Meier curve represents the survival from birth for EJ patients in the Orchard Therapeutics TIGET Natural History Study. The "ERG Amended Model: Weibull" curve is fitted to a Kaplan-Meier curve of EJ patients from GMFC 6 to death and underestimates survival in the model. The "Revised Company Submission: Weibull" curve is fitted to the "empirical" Kaplan-Meier curve of EJ patients' survival from birth.

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Highly Specialised Technologies (HST)
OTL-200 for treating metachromatic leukodystrophy [ID1666]

Dear NICE Technical Team,

Firstly, thank you very much for giving us the opportunity to resolve this issue before the Committee meeting.

Orchard has been in contact with the team who conducted the TTO interviews for the study and can see where the confusion has arisen. Unfortunately, there was an error in the wording used in the clarification response submitted in January. The response to Question B23 in the ERG's clarification questions should have read:

"*If a vignette was rated worse than 'dead' in the TTO task, then the interviewer would turn to the procedure for states considered worse than dead. For such states the lead-time TTO (LT-TTO) valuation procedure was used."*

Orchard sought clarification from the company (highly regarded experts in PROs) to determine the exact TTO and LT-TTO procedures used in the study. The company provided the following information: "*We followed the standard methodology whereby the standard time-trade off method was completed for all states which were better than dead, and lead time method was adopted for those that were worse than dead. In the time trade-off task, participants started all states using the conventional method. The VAS task did not set the precedent for the lead-time task for any health state, even if a participant rated a state as worse than dead in the VAS task. This was an error in the initial clarification which we would like to clarify*."

Furthermore, it appears that an incomplete version of the TTO script used in the study was included in Appendix F in the clarification questions, so please find below the full TTO script which shows each stage for the standard TTO method and the Lead-time method and provides unequivocal evidence that the correct methodology was followed.

Whilst there is not a specific study protocol that explicitly states how the TTO methodology was performed, we hope that the full script provided below which has been used by the team that did the study in several published studies to elicit utilities should suffice to support the assertion that the conventional method was used to establish whether a participant rated a health state worse than death.

Best regards,

Orchard Therapeutics

TIME TRADE-OFF INTERVIEW SCRIPT

Instructions for the interviewer are shown using **CAPITALISED TEXT**. These should **not** be read to the participant.

Instructions for the participant are shown using plain text. These should be read aloud to the participant.

POINTS TO MENTION WHEN STARTING AN INTERVIEW

Thank you for taking the time to participate in this study.

The purpose of this study is to gain an understanding of the impact of living with a health condition. During the interview I will ask you to choose between different descriptions. I will provide you with different descriptions and ask you to think about how good or bad they are.

Before we begin I would like to tell you a few things about the interview.

1. All the information you provide us will remain **confidential**. We only know your first name and in our records that name will be replaced with an ID number.
2. The interview will take **approximately 40-60 minutes** in total to complete. We will ask you to complete some forms as well as answer questions in the interview.
3. Please **take your time** answering the questions.
4. Please remember that there are **no right or wrong answers**. We are interested in your opinion and that is what is important to us. Do not worry about being consistent with previous answers and **feel free to change your mind** if you want to.
5. If you have **any questions throughout the interview** please feel free to ask. We may have to wait until the end of the interview to answer some questions.
6. Your participation in this study is **voluntary,** so if at any time you would like to stop the interview please let me know.
7. Do you have **any questions** before we start?

INTRODUCTION TO HEALTH STATES:

OVERVIEW:

START WITH THE FEELING THERMOMETER, THEN COMPLETE THE TTO EXERCISE. FOR EACH ONE, START WITH A MILD HEALTH STATE (AFTER FULL HEALTH AND DEAD).

We are going to go through two different tasks which we will use to get your views on these health state descriptions. We will explain these tasks at each stage. The purpose of this is to make sure you understand the tasks so please ask me if you have any questions as we go through.

Feeling thermometer

The first method uses this scale.

DISPLAY THERMOMETER AND PLACE ON SCREEN FACING RESPONDENT

MAKE SURE THE RESPONDENT CAN SEE THE FURTHEST END OF THE SCALE

We are going to use this scale to find out **how good or bad** you think each description is.

- The scale runs from 0 to 100.
- Down towards 0 are the very worst or the least preferred descriptions. The further down the scale that you place a description, the worse imaginable health you believe it would be.
- As you go up the scale the descriptions get better until you approach 100 where the very best descriptions could be located. The further up the scale you place a description, the better you believe it would be to experience.
- I am going to ask you to read each description card and **then place it on the scale with an arrow to indicate how good or bad you think it is.**

This is the first description that I would like you to read.

HAND RESPONDENT "FULL HEALTH" CARD
LET RESPONDENT READ CARD

This card describes full health.

Full health is equal to 100 on the scale and so we place it at 100. This is as good as your health can be.

This next card describes the state of being immediately dead.

HAND RESPONDENT "DEAD" CARD
LET RESPONDENT READ CARD

Looking at the scale, where would you place the dead card? Should you decide that you want to move this at any point, you are free to do so.

START WITH A MILD HEALTH STATE

You have the health state descriptions in front of you. I will tell you which one to read one at a time and I would like you to read each card carefully and think about **how good or bad it is**. Then I would like you to place it on the scale. You may decide that a description is worse than dead and decide to place it lower down the scale.

When you read the cards imagine living as the person in the description for the **rest of your life.**

HAND CARD AND ARROW TO RESPONDENT (SHUFFLE CARDS AND PRESENT IN RANDOM ORDER FOR EACH PARTICIPANT)
WAIT FOR RESPONDENT TO COMPLETE RATING
GET NEXT CARD READY

Now read this card and again **rate how good or bad** it is on the scale.

After you have rated a few cards you may wish to **change your ratings.**

Please feel free to adjust if you need to.

CONTINUE WITH ALL CARDS ONE BY ONE TO RESPONDENT- MAKE SURE THEY RATE ALL HEALTH STATE CARDS

BE AWARE THAT SOME PARTICIPANTS WILL INTERPRET THE SCALE THE WRONG WAY ROUND- PLACING THE WORST STATES TOWARDS 100. IF YOU SUSPECT THEY ARE DOING THIS THEN CHECK (**HAVE THEM CONFIRM THAT THEY BELIEVE THE STATES ARE CLOSER TO 'FULL HEALTH' OR 'DEAD' AS APPROPRIATE**).
IF THEY DON'T REALISE THEIR MISTAKE THEN CONTINUE TO THE END OF THE FEELING THERMOMETER TASK AND TERMINATE THE INTERVIEW. BE VERY WARY OF GUIDING PARTICIPANTS OR SUGGESTING TO THEM THAT THEIR ANSWERS ARE IN ANY WAY INCORRECT.

Now that you have the cards on the board, are there any changes you would like to make?

PAUSE UNTIL RESPONDENT INDICATES SATISFACTORY COMPLETION OF ANY REVISIONS

IF THERE ARE ANY STATES RATED AS WORSE THAN DEAD THEN ASK PARTICIPANTS TO CONFIRM THAT THEY ARE WORSE THAN DEAD:

- Now I would like to record your values for each card on the scale.
- Starting at the bottom of the scale, please point to each card in turn and read off the value on the scale that you have given to that card.
- I will write down your answers.

Now we are ready to move onto the next stage in the interview.
Here we will ask you to rate the same description cards, but this time we will use a different method.

REMOVE FEELING THERMOMETER

Health State Valuation Task

In this task we are going to use the same descriptions but using a different method.

In each question I will present you with a series of two choices and ask you to choose the one that you would prefer. If you think the **two choices are about the same tell me** and I will write this down. In order to make the task easier to understand we will use an aid similar to a game board.

PLACE THE TTO BOARD ON THE TABLE.
SET SCALES TO BOTH SHOW ALIVE FOR 10 YEARS

PLACE FULL HEALTH STATE CARD ON LIFE A
PLACE A HEALTH STATE CARD ON LIFE B

The top part of the board is labelled Life A and the bottom part of the board is labelled Life B. These are two choices and we want to know which Life you would prefer. The cards describe the health status of each Life – or what each Life would be like the whole time.

POINT TO THE LIFE A AND LIFE B CARDS

The scale besides each card represents the period of time you can expect to live in this state for. For the purposes of this exercise please imagine that the longest that you can expect to live is 10 years.

Each scale will also show the number of years of life lost due to an early death.

POINT TO SCALE A

The pink colour on the scale shows the number years of Full Health.

RUN FINGER ALONG PINK PART OF SCALE A

You can expect to live 10 years, from today, after that you would die.

POINT TO SCALE A

The years of life lost due to an early death are shown by the black colour.

MOVE THE SLIDER TO DEMONSTRATE A CHANGE IN DURATION.
POINT TO SCALE B

The blue colour here in Life B represents the time you will live in Life B. Think about how good or bad Life B would be for you. In Life B you can expect to live a life as described on the card and you will live for 10 years, from today, followed by death.

Do you understand these ideas?

YES- SET BOTH SCALES TO SHOW ALIVE FOR 10 YEARS AND CONTINUE BELOW
NO- REPEAT PREVIOUS PAGE.

Please read the Full Health card again

ALLOW RESPONDENT TIME TO READ FULL HEALTH CARD

So the duration of Full Health is represented by the pink on the scale.

START WITH A MILD HEALTH STATE.

FOR FIRST HEALTH STATE PLEASE READ OUT ADDITIONAL TEXT IN ITALLICS BELOW, FOR OTHER HEALTH STATES SET SCALE A TO 10 YEARS, GIVE THE NEXT HEALTH STATE CARD TO THE RESPONDENT AND READ TEXT NOT IN ITALICS

This is the first health state description. Please read this card carefully.
Life B is represented by this description.
Let's start the first question by working through it together. The top part of the board represents Life A. The card describes Full Health. The duration of Life A is shown by the pink part of the scale.
POINT TO LIFE A
The scale shows that Full Health will last for 10 years followed by death.
The bottom card and time scale describe Life B. This is the description that you have just read. The bottom time scale, marked in blue shows that this state will last for 10 years followed by death.
POINT TO THE SLIDER ON LIFE A SHOWING THE DURATION

1. Which Life would you prefer, 10 years in Life A or 10 years in Life B, or are they about the same?

IF PARTICIPANT IS UNSURE AT ANY STAGE:
Would you like me to explain this again?

A- MOVE LIFE A SCALE TO 0 YEARS (ALL BLACK) AND CONTINUE

B - ASK "WHY?" MARK RESPONSE (Prefer B: 1.0, and note reason given)
SAME - MARK RESPONSE (Equal: 1.00)

---

2. Now I've changed the Life A time scale to 0 which can be considered as 'dead'. Which Life would you prefer now? 10 years in Life B or being 'dead'?

A or SAME – GO TO LT-TTO INTERVIEW GUIDE (page 10)

B - MOVE SCALE A TO 9.5 YEARS AND CONTINUE

---

3. Now Life A represents 9 years and 6 months of Full Health in total. Which Life would you prefer now? Or are they about the same?

A – MOVE SCALE A TO 0.5 YEARS,
B - MARK RESPONSE (Prefer B: 0.975) GO TO THE NEXT HEALTH STATE
SAME - MARK RESPONSE (Equal: 0.950)

---

4. Now you have 6 months of Full Health followed by death in Life A. Which Life would you prefer? Or are they about the same?

A – MARK RESPONSE (Prefer A: 0.025), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 9 YEARS AND CONTINUE
SAME - MARK RESPONSE (Equal: 0.050)

---

5. Now you have 9 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 1 YEARS AND CONTINUE
B - MARK RESPONSE (Prefer B: 0.925) GO TO THE NEXT HEALTH STATE
SAME – MARK RESPONSE (Equal: 0.900)

---

6. Now you have 1 year of Full Health followed by death in Life A which Life would you prefer? Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.075), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 8.5 YEARS AND CONTINUE
SAME - MARK RESPONSE (Equal: 0.100)

---

7. Now you have 8 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 1.5 YEARS AND CONTINUE
B- MARK RESPONSE (Prefer B: 0.875) GO TO THE NEXT HEALTH STATE
SAME - MARK RESPONSE (Equal: 0.850)

---

8. Now you have 1 year and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.125), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 8 YEARS AND CONTINUE
SAME – MARK RESPONSE (Equal: 0.150)

---

9. Now you have 8 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 2 YEARS,
B - MARK RESPONSE (Prefer B: 0.825) GO TO THE NEXT HEALTH STATE
SAME – MARK RESPONSE (Equal: 0.800)

---

10. Now you have 2 of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.175), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 7.5 YEARS AND CONTINUE
SAME – MARK RESPONSE (Equal: 0.200)

---

11. Now you have 7 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 2.5 YEARS,
B - MARK RESPONSE (Prefer B: 0.775) GO TO THE NEXT HEALTH STATE
IF HEALTH STATES SAME – MARK RESPONSE (Equal: 0.750)

---

12. Now you have 2 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MARK RESPONSE (Prefer A: 0.225), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 7 YEARS AND CONTINUE
SAME – MARK RESPONSE (Equal: 0.250)

---

13. Now you have 7 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 3 YEARS
B - MARK RESPONSE (Prefer B: 0.725) GO TO THE NEXT HEALTH STATE
SAME – MARK RESPONSE (Equal: 0.700)

---

14. Now you have 3 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.275), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 6.5 YEARS AND CONTINUE
SAME – MARK RESPONSE (Equal: 0.300)

---

15. Now you have 6 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 3.5 YEARS AND CONTINUE
B- MARK RESPONSE (Prefer B: 0.675) GO TO THE NEXT HEALTH STATE
SAME – MARK RESPONSE (Equal: 0.650)

---

16. Now you have 3 years and 6 months of Full Health followed by death in Life A , which Life would you prefer? Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.325), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 6 YEARS AND CONTINUE
SAME – MARK RESPONSE (Equal: 0.350)

---

17. Now you have 6 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 4 YEARS,
B - MARK RESPONSE (Prefer B: 0.625) GO TO THE NEXT HEALTH STATE
SAME – MARK RESPONSE (Equal: 0.600)

---

18. Now you have 4 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.375), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 5.5 YEARS AND CONTINUE
SAME – MARK RESPONSE (Equal: 0.400)

---

19. Now you have 5 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A – MOVE SCALE A TO 4.5 YEARS,
B - MARK RESPONSE (Prefer B: 0.575) GO TO THE NEXT HEALTH STATE
SAME – MARK RESPONSE (Equal: 0.550)

---

20. Now you have 4 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.425), GO TO THE NEXT HEALTH STATE.
B - MOVE SCALE A TO 5 YEARS AND CONTINUE
SAME – MARK RESPONSE (Equal: 0.450)

---

21. Now you have 5 years of Full Health followed by death in Life A, which Life would you prefer?

Or are they about the same?

A - MARK RESPONSE (Prefer A: 0.475) GO TO THE NEXT HEALTH STATE

B – MARK RESPONSE (Prefer B: 0.525), GO TO THE NEXT HEALTH STATE.
SAME - MARK RESPONSE (Equal: 0.500)

LEAD-TIME TTO INTERVIEW GUIDE

Given that this is how you feel about this description I am going to ask you a bit more about it using a slightly different method

SHOW THE LT-TTO BOARD (OTHER SIDE OF BOARD).
SET LIFE A TO SHOW ALIVE FOR 10 YEARS
PLACE FULL HEALTH STATE CARD ON PLACEHOLDER TO THE LEFT
PLACE HEALTH STATE CARD ON PLACEHOLDER TO THE BOTTOM RIGHT

On the board you can see two scales both showing 20 years. The top scale is labelled Life A and the bottom scale is labelled Life B. As before, we want to know which you prefer, imagining that you are the individual described.

Please imagine that in the top scale, Life A, you would live for 10 years, from today, in the pink Full Health state described on the left, and then you would die. In the bottom scale, Life B, you would live for 10 years, from today, in the pink Full Health state described on the left, followed by 10 years as the person described on the bottom, and then you would die.

Do you understand these ideas?

WITH THE MARKER FOR LIFE A SET TO 10 YEARS

3. Now, do you prefer Life A, Life B, or are they about the same?

A – MOVE SCALE A TO 0 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: 0.0) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME – MARK RESPONSE (Equal: 0.0)

---

4. Now I've changed Life A to 0 which can be considered as 'dead'. Which Life do you prefer now or are they about the same?.

A – MARK RESPONSE (Prefer A: -1.0) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B- MOVE SCALE A TO 9.5 YEARS AND CONTINUE.

SAME – MARK RESPONSE (Equal: -1.000)

---

5. Now you have 9 years and 6 months of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

A - MOVE SCALE A TO 0.5 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.025) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME – MARK RESPONSE (Equal: -0.050)

---

6. Now you have 6 months of Full Health followed by death in Life A, which Life would do you prefer or are they about the same?

A – MARK RESPONSE (Prefer A: -0.975) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 9 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.950)

---

7. Now you have 9 years of Full Health followed by death in Life A , which Life would you prefer or are they about the same?

A - MOVE SCALE A TO 1 YEAR AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.075) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)

SAME – MARK RESPONSE (Equal: -0.100)

---

8. Now you have 1 year of Full Health followed by death in Life A, which Life do you prefer or are they about the same?

A – MARK RESPONSE (Prefer A: -0.925) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 8.5 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.900)

---

9. Now you have 8 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A - MOVE SCALE A TO 1.5 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.125) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME LIFE – MARK RESPONSE (Equal: -0.150)

---

10. Now you have 1 year and 6 months of Full Health followed by death in Life A, which Life do you prefer, or are they about the same?

A – MARK RESPONSE (Prefer A: -0.875) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 8 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.850)

---

11. Now you have 8 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

A - MOVE SCALE A TO 2 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.175) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME – MARK RESPONSE (Equal: -0.200)

---

12. Now you have 2 years of Full Health followed by death in Life A , which Life would you prefer or are they about the same?

A – MARK RESPONSE (Prefer A: -0.825) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 7.5 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.800)

---

13. Now you have 7 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A - MOVE SCALE A TO 2.5 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.225) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
IF HEALTH STATES SAME – MARK RESPONSE (Equal: -0.250)

---

14. Now you have 2 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A – MARK RESPONSE (Prefer A: -0.775) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 7 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.750)

---

15. Now you have 7 years of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A - MOVE SCALE A TO 3 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.275) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME- MARK RESPONSE (Equal: -0.300)

---

16. Now you have 3 years of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A – MARK RESPONSE (Prefer A: -0.725) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 6.5 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.700)

---

17. Now you have 6 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A - MOVE SCALE A TO 3.5 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.325) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME – MARK RESPONSE (Equal: -0.350)

---

18. Now imagine you have 3 years and 6 months of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

A – MARK RESPONSE (Prefer A: -0.675) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 6 YEARS AND CONTINUE.
IF HEALTH STATES SAME – MARK RESPONSE (Equal: -0.650)

---

19. Now you have 6 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

A - MOVE SCALE A TO 4 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.375) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME – MARK RESPONSE (Equal: -0.400)

---

20. Now you have 4 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

A – MARK RESPONSE (Prefer A: -0.625) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 5.5 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.600)

---

21. Now you have 5 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A - MOVE SCALE A TO 4.5 YEARS AND CONTINUE.
B - MARK RESPONSE (Prefer B: -0.425) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
SAME – MARK RESPONSE (Equal: -0.450)

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22. Now you have 4 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A – MARK RESPONSE (Prefer A: -0.575) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B-MOVE SCALE A TO 5 YEARS AND CONTINUE.
SAME – MARK RESPONSE (Equal: -0.550)

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23. Now you have 5 years of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

A - MARK RESPONSE (Prefer A: -0.525) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
B – MARK RESPONSE (Prefer B: -0.475), GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)
IF HEALTH STATES SAME - MARK RESPONSE (Equal: -0.500) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)

AT THE END OF THE INTERVIEW, CHECK PARTICIPANT'S AWARENESS THAT THEY RATED THIS STATE AS WORSE THAN DEAD AND WHETHER THIS IS THEIR ACTUAL VIEW.
THANK THE PARTICIPANT FOR HIS/HER TIME AND ASK IF THEY HAVE ANY QUESTIONS.

CONFIDENTIAL APPENDIX
Evidence Review Group's Report
OTL-200 for treating metachromatic leukodystrophy

ECM 1 ERG Addendum

1 Overview of key outstanding uncurtains and committee preferences

1.1 Population

Committee preference: Further exploration of uncertainties in population distribution

ERG comment: The ERG acknowledges that there is significant uncertainty in the distribution of patients across subtypes and notes the insights from the clinical experts, which indicated that symptomatic early juvenile patients may be diagnosed and treated in the absence of an older affected sibling. The ERG, however, considers the proposed ERG distributions to be the most reasonable and to make the best use of the limited available data. While diagnosis in the absence of older affected sibling is a possibility, the likelihood of this occurring early enough to administer OTL-200 is very small. This is due to the aggressive nature of MLD, which typically progresses quickly following onset of symptoms. The mean time between symptom onset and the receipt of a diagnosis in juvenile patients was stated to be 2.9 years in the company submission, with another source suggesting 14.5 months (not subtype-specific). This means it is unlikely that an index case will be diagnosed before substantial progression of symptoms in current practice.

In the additional scenario analysis reported in Section 2 the ERG presents exploratory analysis using the company's suggested distribution, but retains the ERG distribution for the alternative base-case.

1.2 Response rates

Committee preference: Further exploration of the potential for patients to stabilise in GMFC 3 and 4

ERG comment: As outlined in the ERG report, the distinction between stable and unstable partial responders is not clear on the basis of the presented evidence. There appear to be few patients who would meet the criteria for being a stabilised partial responder (initial decline followed by long-term stabilisation) and equally limited evidence on whether patients will continue to experience progression of disease. Given this uncertainty, the ERG base-case took a conservative approach which aligned with the company's base-case, assuming that a proportion of patients would continue to progress, albeit more slowly than an untreated patient.

Expert testimony elicited at the committee meeting, however, suggested this approach may be overly pessimistic and indicated an expectation that the majority, if not all patients would stabilise. It was further explained that stabilisation would likely occur over broader set GMFC health states than currently modelled where stabilisation is restricted to GMFC 0, 1 and 2. The biological rationale for this approach (as understood by the ERG) is that underlying damage occurring prior to recovery of ARSA activity will to continue to manifest for substantial periods of time after infusion, resulting in the appearance of continued loss of motor and other skills.

To explore these uncertainties the ERG presents several scenarios considering alternative assumptions about the response rate and distribution of GMFC states in which patients stabilise. In the first scenario (Scenario 2a) the ERG revises the response rates such that all patients previously classified by the ERG as unstable partial responders are assumed to become stabilised partial responders. Stabilisation is assumed to occur in GMFC 3 and 4, reflecting the clinical opinion that patients would stabilise across a broader range of GMFC health states than currently modelled. In scenario 2b and 2c this line of thought is extended so that now all stabilised partial responders are assumed to stabilise in GMFC 4. This is not intended to represent a realistic scenario, but is illustrates the impact of patients stabilising in health states associated with a very poor HRQoL. Scenario 2b and 2c are distinguished by the utility set used; in scenario 2b the ERG utility set is used and in 2c the LI utility set is used, the latter representing a more pessimistic view of the quality of life of patients in GMFC 4.

1.3 Utility Set

Committee preference: Exploration of alternative company utility set.

ERG comment: As outlined in our report the ERG has substantive concerns regarding the utility set proposed by the company, specifically concerning the elicitation methods used and the face validity of the values generated. In response to this critique, the company has provided a revised utility set in which the original utility set has been rescaled to better align with the range of values encompassed by the UK EQ-5D 3L value set. The rescaled utility set is presented in Table 1.

Table 1 Company rescaled utility set

GMFC Health States	Normal cognition	Moderate cognitive impact	Severe cognitive impact
GMFC0	General population	0.85	0.41
GMFC1	0.90	0.77	0.28
GMFC2	0.81	0.56	0.35
GMFC3	0.48	0.17	-0.11
GMFC4	0.04	-0.22	-0.21
GMFC 5	NR*	-0.23	-0.40
GMFC6	NR*	-0.36	-0.40

* Values for these health states were not provided.

While the ERG recognises the pragmatic advantages of the company's proposal, the ERG in principle does not consider rescaling to be an appropriate solution to the issues raised in the ERG report. Specifically, the values are still based on a non-reference case approach that has not been justified and is subject to the methodological limitations outlined in the ERG's report, including issues relating to the content and construction of the vignettes; the ability of healthy adults to comprehend the life of a

child with MLD, or the interaction between the physical and cognitive disease burden; and the lack of context given as part the elicitation exercise.

Importantly, the revised utility set retains a significant decrement associated with loss of cognitive capacity. The ERG has continued concerns about the application of decrements to reflect loss of cognitive skills and re-emphasises that the relationship between cognitive ability and HRQoL is likely to be mediated significantly by loss of motor skills as borne out by several publications cited in the ERG's report. The ERG also considers that there is a significant possibility that the relationship between the impact of cognitive impairment and motor skills may not be monotonic. This is because in the worst health states loss of cognition is so complete, it limits an individual's awareness of their condition. This contrasts with notionally less severe states (GMFC 3 and 4) which are characterised by significant loss of motor skills, but where patients are likely to have much greater awareness of their environment, pain, and broader symptoms, with associated consequences in terms of individuals' mental well-being.

In addition to these objections to the rescaled utility set, the ERG also notes that there are a number of logical inconsistencies in the revised values. Specifically, utility values for GMFC 4 with moderate cognitive impact (MCI) is predicted to be worse than the same state with serious cognitive impact (SCI) and GMFC 1 with SCI is predicted to be worse that GMFC 2 with SCI. The impact of cognitive impairment also varies very significantly across the health states, ranging from an increment of 0.01 to a decrement of 0.49. This does not make sense given the company's previous position of an additive effect. Furthermore, the magnitude of the decrement does not appear to change in any kind of consistent pattern, serving to undermine the face validity of the utility set. These inconsistencies are likely due to the company's approach to rescaling; however, the ERG cannot comment on the methods used as no details were provided.

Given the highlighted limitations of the rescaled utility set, the ERG is not convinced that this represents an improvement on either the original utility set provided by the company or the alternative values used by the ERG in its utility set which removed the cognitive decrements. The impact of this revised utility set is, however, explored in scenario analysis to allow the committee to consider its impact. In these scenarios, assumptions made in the ERG base-case regarding decrements associated with loss of cognitive function and impact of OTL-200 on cognitive ability are relaxed to align with company's base-case so as to illustrate the full impact of the alternative utility set.

1.4 Stabilisation

Committee preference: Stabilisation for an average of 20 years.

ERG comment: As acknowledged by the Committee, the permanence of the treatment effect represents a key uncertainty and driver of model outcomes. The lack of long-term data and clinical experience, however, means the plausibility of any alternative scenarios is unknown.

At the committee meeting the company and the clinical experts were keen to emphasise the similarity of OTL-200 to other gene therapies and the limited scope for graft failure. However, as outlined in the ERG report, there are factors unique to all such technologies which may impact the long-term durability of the treatment effect. The mode of action in OTL-200 is itself unique amongst available gene therapies, and the mechanism of action is not fully understood.

Importantly, the ERG re-emphasises that the presented data is also not wholly supportive of the concept of permanent stabilisation. The ERG specifically highlights the fact that several patients appeared to have experience delayed progression following a long period of stability. Furthermore, there is evidence of continued decline in relevant biomarkers, as well as a suggestion that OTL-200 does not prevent disease progression across all systems equally. The declining levels of CSF ARSA activity observed in several late infantile and pre-symptomatic early juvenile patients are of specific concern, given the EMA's expectations that continued ARSA activity is a prerequisite for the continuation of treatment benefits.

The ERG presents further exploratory analyses using the committee's preferred assumption of 20 year average stabilisation, as well as additional scenario analysis considering 10 year, 15 year and permanent stabilisation.

2 Additional scenario analysis

Tables 2 and 3 present additional scenario analysis considering the assumptions discussed above. Table 2 uses the ERG base-case as a starting point and explores specific assumptions relating to the population distribution, response rates, utility set and stabilisation assumptions. Table 3 revises the ERG base using Scenario 2a and Scenario 4 from Table 2. Further scenario analyses are then presented using this alternative base-case as a starting point. Markov traces for the ERG base-case and alternative base-case are also included in Appendix A to aid committee understanding. All presented scenarios include the PAS discount available for OTL-200.

Table 2 ERG base-case results and selected scenarios.

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
ERG base-case																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 1: Apply company population distribution																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 2a: Assume all patients model as unstable in ERG base-case stabilise in GMFC 3 and 4																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 2b: Assume all patients not classified as full responders stabilise in GMFC 4																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 2c: Assume all patients not classified as full responders stabilise in GMFC 4 plus LI utility set																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 3: Company revised utility set																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 4: Stabilisation 20 years																
BSC	[redacted]															

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]															

Table 3 Alternative base-case results and select scenario analysis

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
Alternative base-case																
BSC	[redacted]															
OTL-200	[redacted]															
Alternative base-case scenario 1: Apply company population distribution																
BSC	[redacted]															
OTL-200	[redacted]															
Alternative base-case scenario 2a: 10-year stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															
Alternative base-case scenario 2b: 15-year stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															
Alternative base-case scenario 2c: Permanent stabilisation																
BSC	[redacted]															

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 3: Company revised utility set																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 4: Assume all patients not classified as full responders stabilise in GMFC 4																
BSC	[redacted]															
OTL-200	[redacted]															

Appendix A: Markov traces

ERG base-case

Figure 1: Pre-symptomatic late infantile: BSC

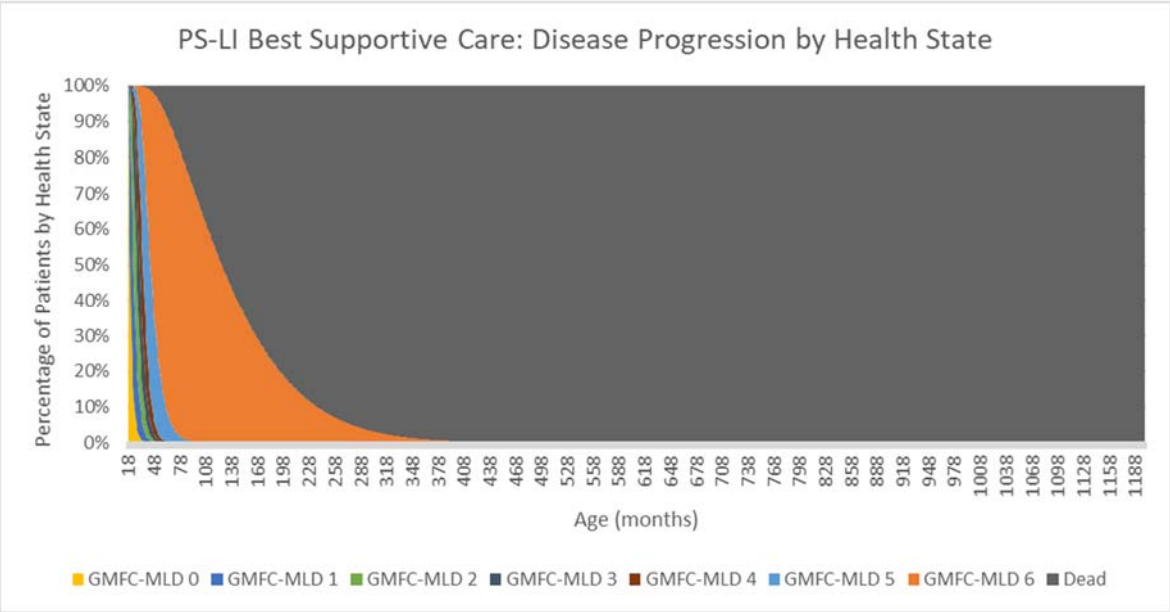


Figure 2: Pre-symptomatic late infantile: OTL-200

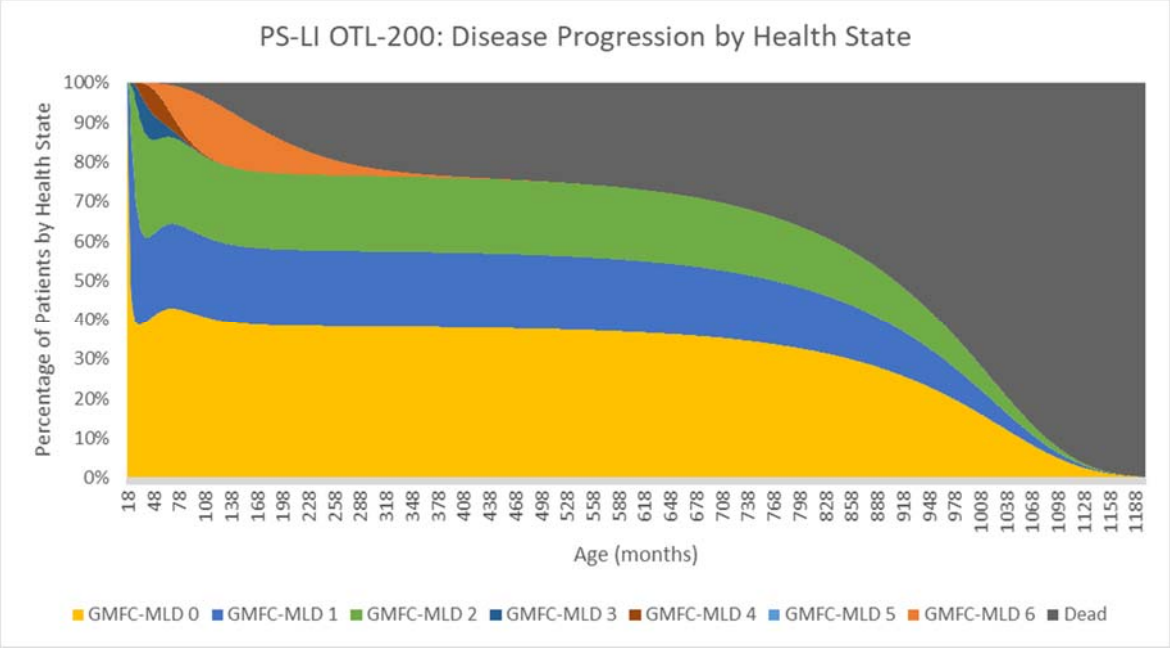


Figure 3: Pre-symptomatic early juvenile: BSC

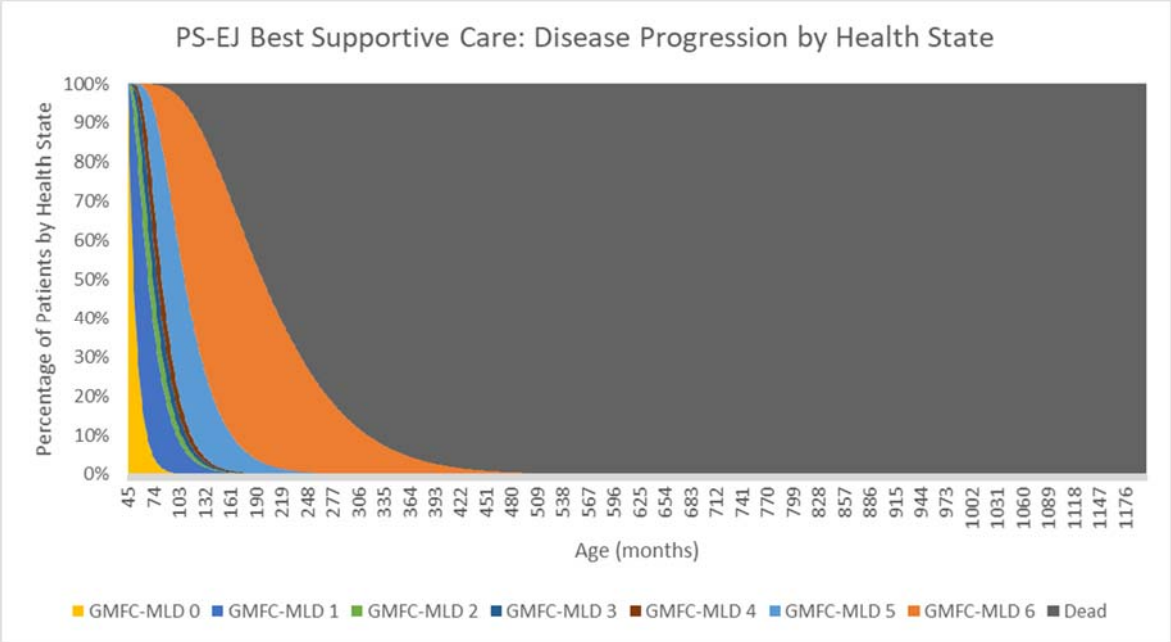


Figure 4: Pre-symptomatic early juvenile: OTL-200

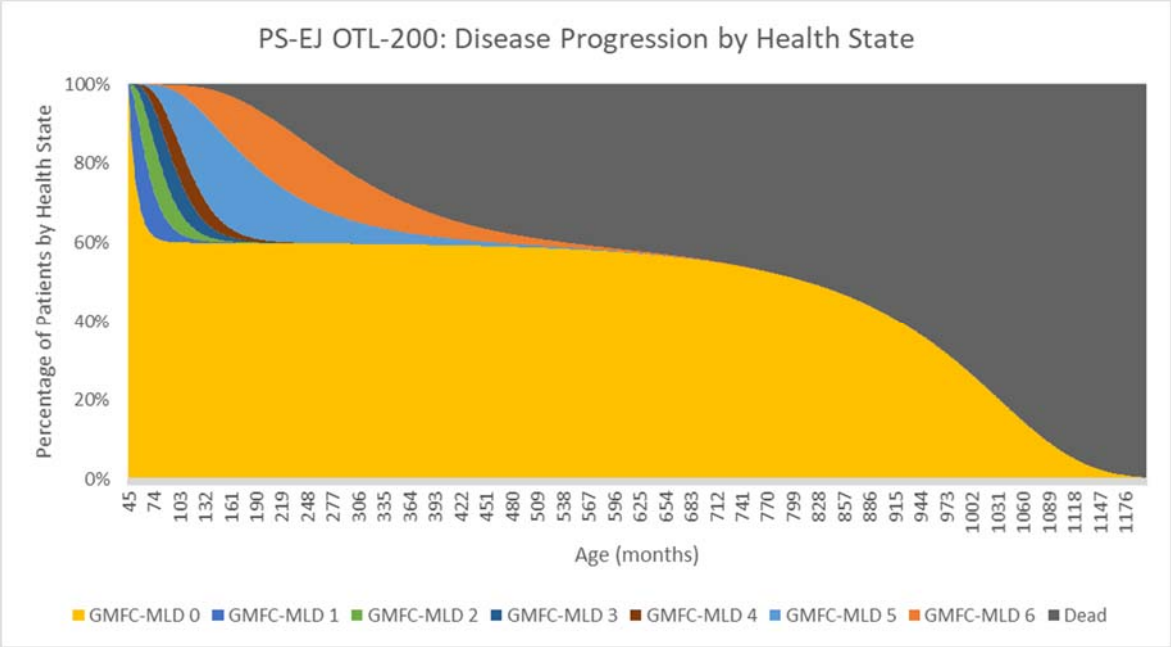


Figure 5: Symptomatic early juvenile: BSC

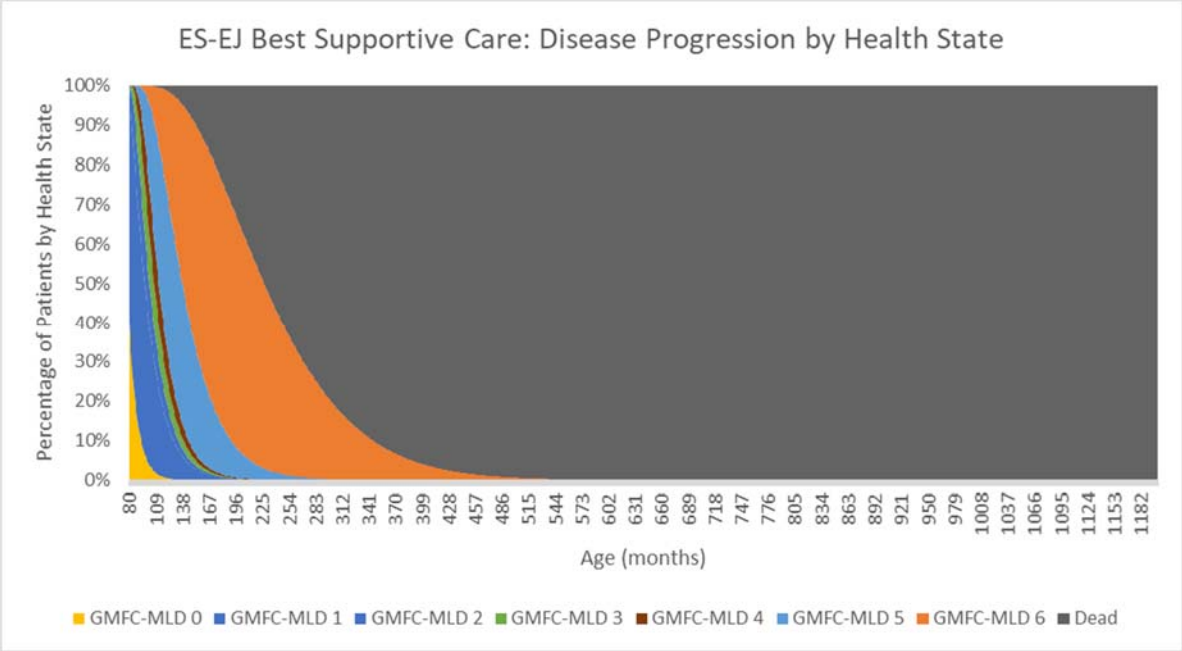
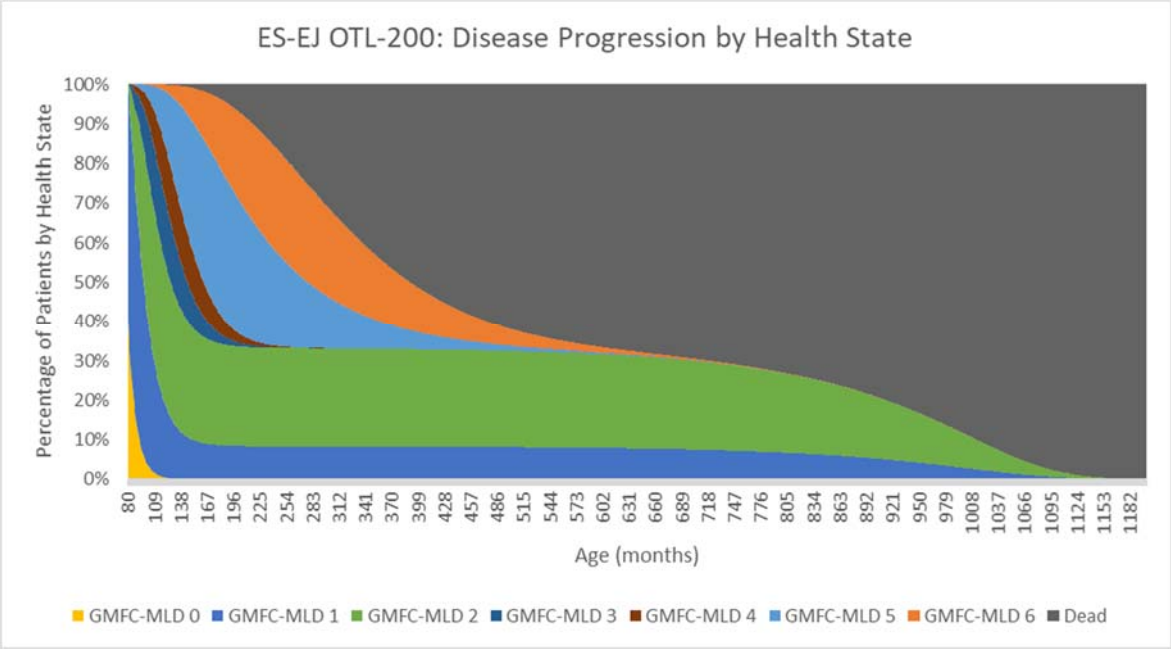


Figure 6: Symptomatic early juvenile: OTL-200



Alternative base-case

Figure 7: Pre-symptomatic late infantile: BSC

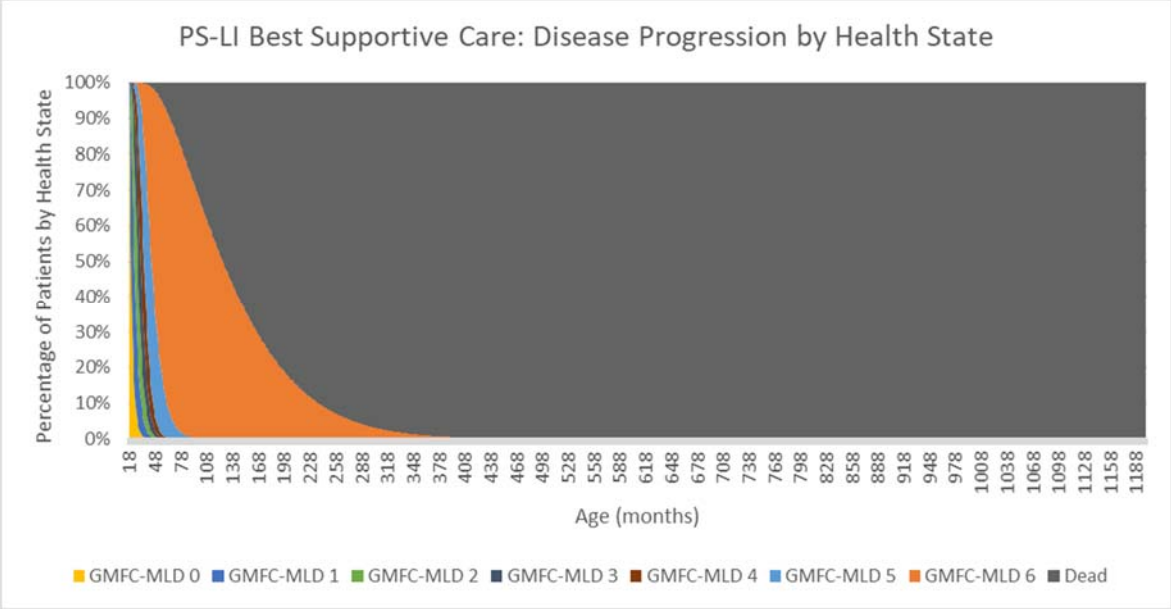


Figure 8: Pre-symptomatic late infantile: OTL-200

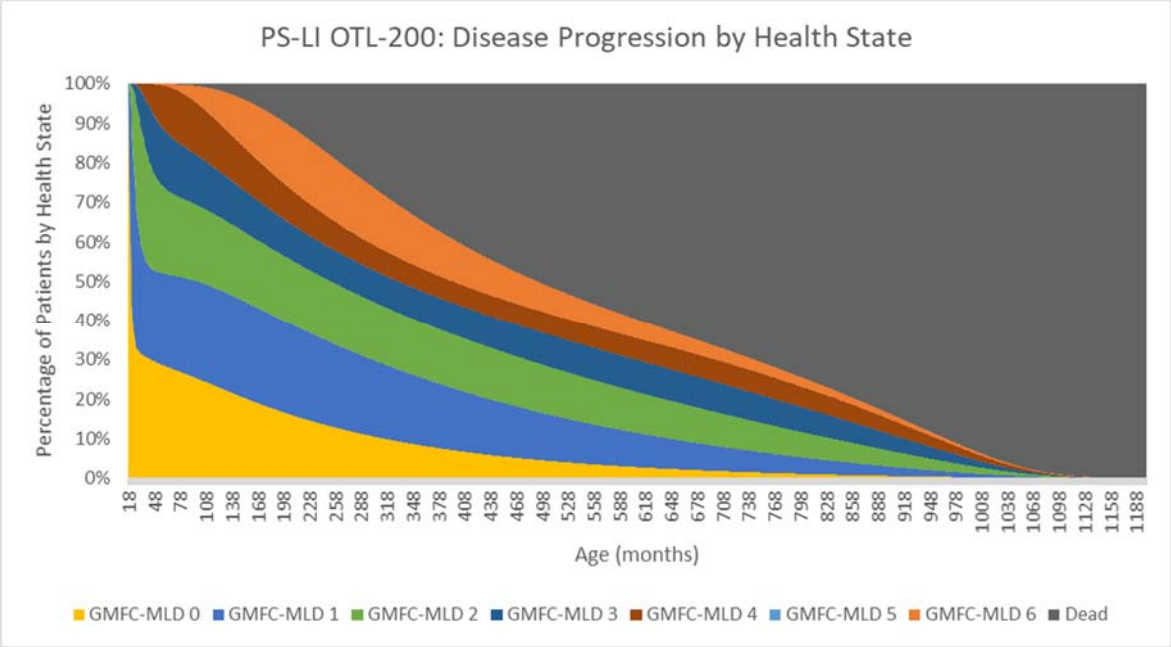


Figure 9: Pre-symptomatic early juvenile: BSC

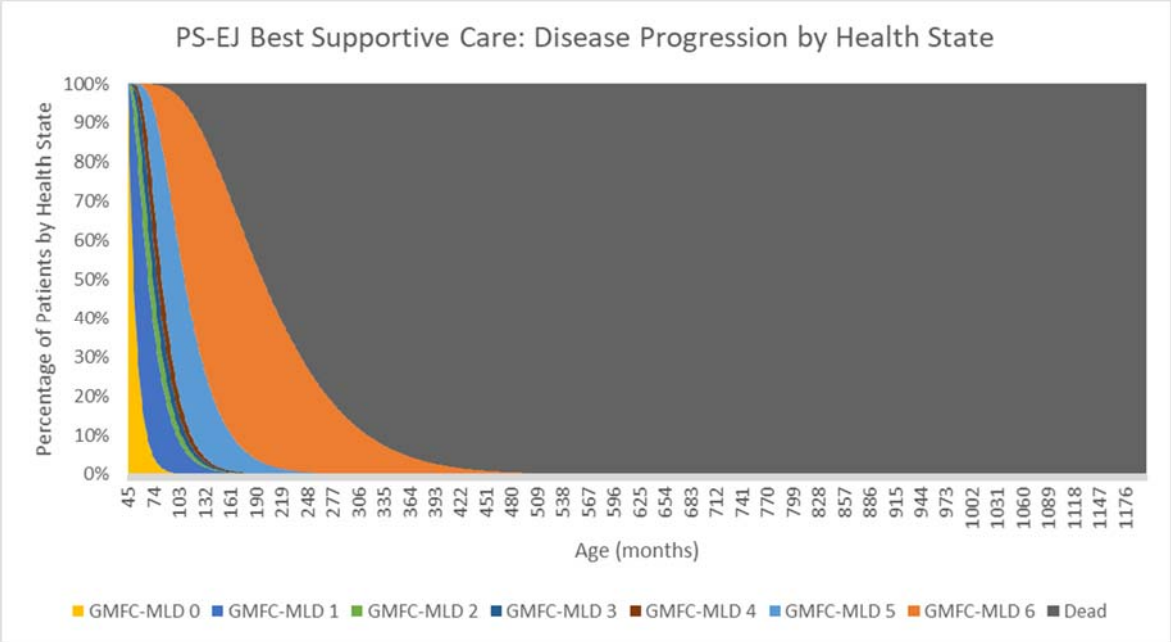


Figure 10: Pre-symptomatic early juvenile: OTL-200

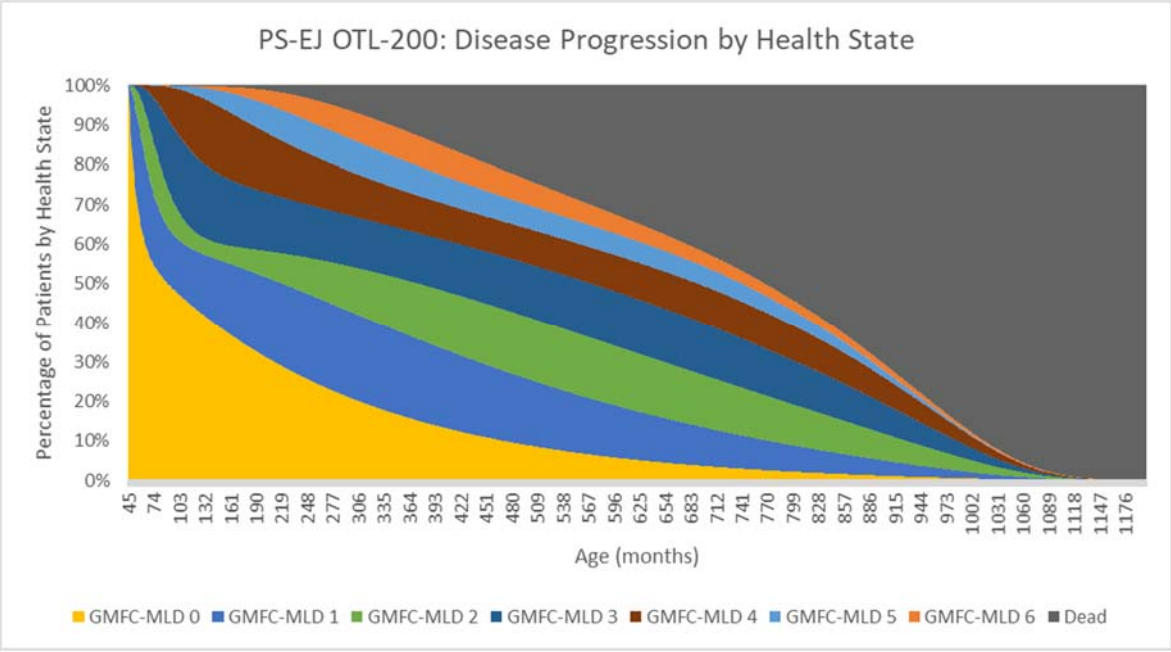


Figure 11: Symptomatic early juvenile: BSC

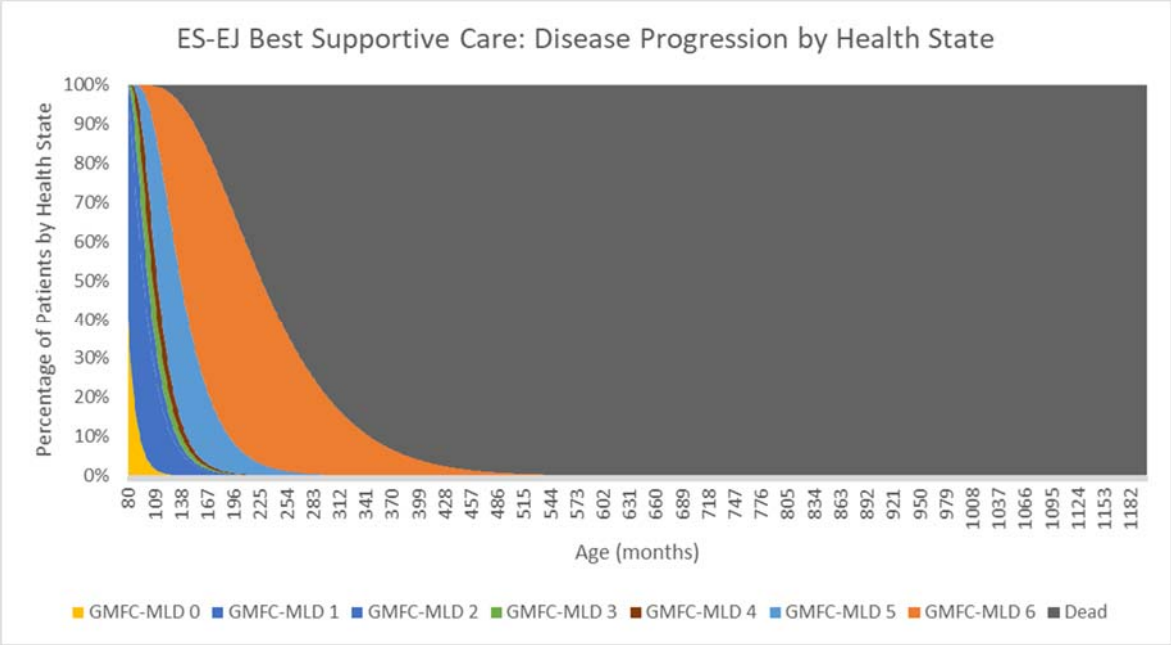
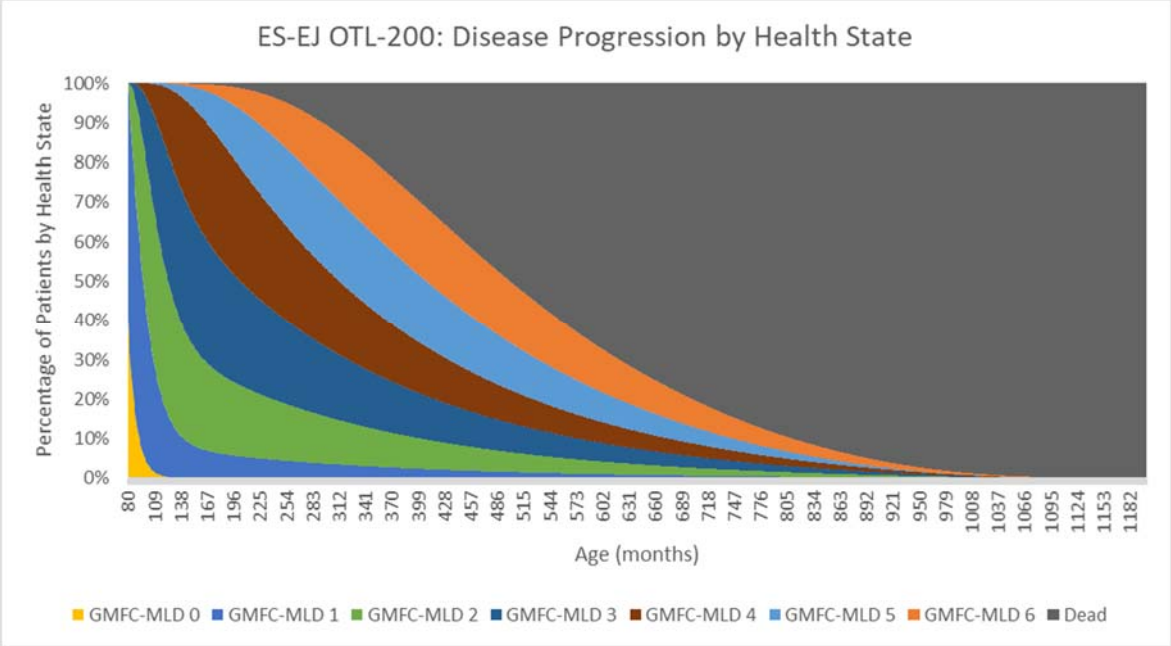


Figure 12: Symptomatic early juvenile: OTL-200



Appendix B: Composition of early symptomatic Early Juvenile (ES-EJ) subgroup

Early Juvenile defined as 1 null allele and 1 residual allele (0/R genotype) or less frequently 2 residual alleles (R/R genotype) and **age of symptom onset between 30 months and 6 years.**

GMFC plots	Baseline information from CSR	ERG comments
	[redacted]	Patient was [redacted], so probably reasonable to include.
	[redacted]	
	[redacted]	Patient was [redacted], but may have been recruited before age 7. [redacted], so unclear how onset was diagnosed.
	[redacted]	Patient was [redacted], so unclear how onset was determined. This is the patient noted in report and slides as being very late to treatment. Unclear if this is really an EJ case without fuller data
	[redacted]	

[redacted]	[redacted]	Patient was excluded due to [redacted]. This was valid.
[redacted]	[redacted]	Patient was excluded due to low IQ. But borderline [redacted] at time of treatment, but patient had little follow-up data
[redacted]	[redacted]	Patient was excluded by the company, but deemed eligible by the ERG (information in CSR confirms our position)

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Company response to ERG Addendum

Table of Contents

OTL-200 for treating metachromatic leukodystrophy [ID1666]

Company response to ERG Addendum

Orchard welcomes the opportunity to respond to the additional analyses conducted by the ERG and presented in the ERG's Addendum report. In this response document, the company addresses the issues raised by the committee (outlined in the correspondence from NICE) and has provided additional evidence to support the company's position on the issues raised.

Executive Summary

Orchard has provided an updated data analysis to fulfil the request from NICE around longer-term data. This analysis has only recently been performed and is based on the December 2019 data cut (i.e., follow-up visits up to December 2019). This data cut was originally specified to help respond to questions or data requests from the EMA during their assessment last year. It provides approximately 5 years follow-up data for all indicated patients in the pivotal (study 201222; n=16) and CO2 (CUP 207394; n=1) studies. Compared to the data included in the company submission, this equates to an additional 2 years' worth of data for all PS-EJ and ES-EJ patients as well as a significant proportion of the LI patients. However, it should be specified that it does not include data from the two expanded access programs (CUP 206258 and HE205029), as validated longer-term data available beyond that included in the original company submission were not available. Most of these data have only recently been analysed and hence were not available to the market access team for incorporation into our company submission in November 2020.

No new data for the cryopreserved formulation exists as the November 2019 data cut included in the company submission represents the latest validated data currently available, however the company has included data for similar analogues for the committee's consideration.

As a result of the new analysis, response categories have been updated specifically for the ES-EJ and PS-EJ patients, as the new analysis includes data from all patients with these MLD variants. Furthermore, the company has now been able to calculate the progression modifiers for ES-EJ patients for GMFC-MLD1-2 and 2-3. Given the previous estimates were based on a shorter duration of follow-up or Delphi panel opinion/assumption, Orchard considers that these updated estimates provide a more accurate representation of long-term treatment effect.

Whilst the company ascertains that the original utilities presented in the company submission accurately represent the quality of life of MLD patients at different stages of the disease, in order to facilitate the decision making by NICE, Orchard has presented two alternative utility value sets for the committee's consideration: (a) rescaled utilities which address the concerns raised around some of the severe health state values being worse (more negative) than the floor value of the EQ-5D-5L and the logical inconsistencies the ERG raised in the Addendum report. The rescaled values align with the utility values reported in HST12 for CLN2, which clinical experts have indicated is of lesser disease severity than MLD. (b) A utility 'top-up' - Due to the ERG's concerns around the magnitude of the cognitive decrement, the company has included a top-up on the normal cognitive function utilities for the juvenile heath states and assigned this to OTL-200 patients to reflect the benefits beyond motor function that treated patients have compared to natural history, such as reductions in seizures, pain, improved cognitive function and improvements in feeding. Best supportive care patients were assigned the normal cognitive function utilities for the juvenile health states without the top-up.

Orchard is uncertain of the rationale for choosing a 20-year duration for disease stabilisation, as the mechanism of action (MoA) of OTL-200 supports long-term stabilisation greater than this. The company recognises that based on the evaluation of other gene therapies, the

committee may have had some reservations about the durability of effect. However, given the unique modality of ex vivo gene therapies, these reservations do not apply to OTL-200 for the following reasons:

(i) OTL-200 uses a retroviral vector which allows the corrected gene to be integrated directly into the genome of the target cell, where they can be replicated whenever the cell divides or differentiates. As such, the added corrected gene is subsequently passed on to all of its progeny. (Mali, 2013). This is unlike in vivo gene therapies which do not integrate directly into the genome and as such may not be able to pass the corrected gene to daughter cells following cell division.

(ii) In addition, the self-renewal capability of HSPCs suggests that once the gene corrected HSPCs successfully engraft in the brain, there would be a steady supply of the genetically corrected cells and their progenies for the patient's lifetime. (Larochelle and Dunbar, 2013, Naldini, 2019)

Furthermore, the MoA of OTL-200 is broadly based on the principle of allogenic haematopoietic stem cell transplants (HSCT) which have shown ongoing durability of effect for metabolic patients beyond 30 years.. This is supported by experienced UK clinical experts in HSCT procedures. Furthermore, HSCT has been used for over 50 years to treat patients with several diseases and has shown to be effective in preventing disease progression. In addition, the MoA of OTL-200 enables the direct integration of the corrected gene into the genome unlike in vivo gene therapies.

Finally, Orchard has included an alternative base case, which the company hopes can be a suitable basis for NICE decision making. This alternative company base case is based on the "alternative ERG base case" with the following revisions: (1) normal juvenile utilities from the company revised utility set (rescaled utility) plus top-up for OTL-200 treated patients as discussed above; (2) 50-year disease stabilisation to reflect the maximum time frame HSCT has been used to effectively treat patients; (3) updated response rates and progression modifiers as discussed above.

All analyses are based on the updated PAS price [redacted] available for OTL-200, which represents a reduction of [redacted] on the list price and an additional [redacted] less than the previously agreed PAS price.

1. Updated Data

In response to the request from NICE, Orchard have provided results from a recent data analysis based on a December 2019 data cut (i.e., visits up to December 2019). These outputs are detailed in Appendix A. These data provide at least 5 years of follow-up for all patients in the Pivotal study (201222) and CO2 (CUP 207394) (i.e., an additional ~2 years' of data for 17 patients: 8 LI; 4 PS-EJ; and 5 ES-EJ patients, compared to what was included in the company submission). This data has only recently been analysed and hence was not available to incorporate into our company submission.

This recent data analysis does not include longer term data from the other expanded access studies (CUP 206258 and HE205029), as validated longer-term data from these studies are not currently available. Appendix A provides efficacy results from this more recent data analysis (based on visits up on to Dec 2019) showing that patients classified as stabilisers saw improvements or stabilisation across all relevant clinical outcome measures (GMFC, GMFM and DQ performance) and the majority of disease markers (ARSA CSF, MRI and NCV). While those classified as having disease progression showed continued worsening of some of the clinical outcomes and disease markers, but still experiencing better outcomes than natural history patients.

1.1 Updated data analysis

The data analysis that formed the basis for the submission to NICE is the most comprehensive data set the company has, as it contains data for all eligible patients treated with OTL-200 in the clinical trial program, which is why it was used. However, Orchard has investigated the possibility of providing a more recent data analysis to help eliminate some of the uncertainty the committee has around the distinction between stable and unstable partial responders. The most recent data cut off point is December 2019, as data collected from visits after this time point have not been verified due to ongoing COVID restrictions preventing monitoring and source data verification at the site in Milan (Milan was a COVID-19 hot-spot during the early days of the pandemic in 2020). This data cut-off was originally chosen to allow the company to respond to any EMA data requests during the regulatory approval process last year. The EMA requested a few ad hoc bespoke analyses during 2020, mostly around safety and some of the ES-EJ patient data.

Therefore, Orchard has been able to perform a further comprehensive and bespoke data analysis in May 2021 upon request by NICE, based on the December 2019 data cut. This provides an additional ~2 years' worth of follow-up data for 17 patients on top of what has already been reported. Orchard would like to make the committee aware that these data have only just been analysed, and due to the constraints of the timeline for this response, the company has not been able to fully validate these analyses, nor will it be able to do so prior to submission of this document. However, Orchard felt it was important to include any further available data to assist the committee in it's decision making.

1.2 Impact of the updated data analysis on ERG corrected model

The May 2021 data analysis has been used to inform the classification of response (i.e. proportion of patients who are full responders, stable partial responders, and unstable partial responders etc.) for the PS-EJ (n=4) and ES-EJ patients (n=5) as data were available for all these patients in the updated data set. A re-analysis of the available PS-LI patients (8 out of 15) was also performed. However, although the proportion of full responders and partial responder stabilisers in the updated analyses was greater than the previous estimates used in the model by the ERG, no further updates were made to the LI response rates, as the

updated analyses does not include data from all LI patients (i.e., 7 out of 15 LI patients who were in the 2 expanded access programs were not included in this data cut off point).

Orchard would like to make the committee aware that the updated data analysis for the 8 LI patients shows that [redacted] patients are either full responders or partial responders – stabilising at GMFC-MLD 1 and 2; however, the company recognises that there are not follow-up data for the other 7 LI patients and is therefore willing to accept the ERG scenario for these LI patients (version 1 and 3 in the ERG's corrected model).

The updated data analysis (see Appendix A) provides at least 5 year follow up data for the early juvenile population and shows that for PS-EJ, [redacted] of patients are full responders, stabilising at GMFC-MLD 0 and with normal values across a broad range of outcome measures. The remaining [redacted] have continued disease progression, albeit at a slower rate than natural history (NHx), therefore experiencing better outcomes than natural history patients.

For ES-EJ, 5-year follow-up data show that [redacted] have continued disease progression but at a slower rate than natural history patients (NHx). In addition to being able to classify the response status of the ES-EJ population (i.e. determine if they are full responders or partial responders), the company has now been able to calculate progression modifiers for the ES-EJ patients who have continued disease progression, which were previously based on expert clinical opinion. Analysis of the data show that [redacted] It was not possible to estimate progression modifiers for transitions between GMFC-MLD 3 and 4 and beyond as only one patient had progressed to 4 and none beyond within the trial period so far.

Orchard considers that analyses based on the updated response data and the newly derived progression modifiers, reinforces the evidence base for decision making.

On a separate but important point, in the ERG corrected model, the progression modifiers for OTL-200 treated ES EJ patients between GMFC 0-1 and GMFC 1-2 were set at a rate of [redacted] respectively, which provides a clinically implausible situation where patients treated with OTL-200 progress faster than natural history. There is no evidence to support this assumption, and the company has therefore set any progression modifiers [redacted] in the ERG model to [redacted]

1.3 Cryopreserved formulation of OTL-200

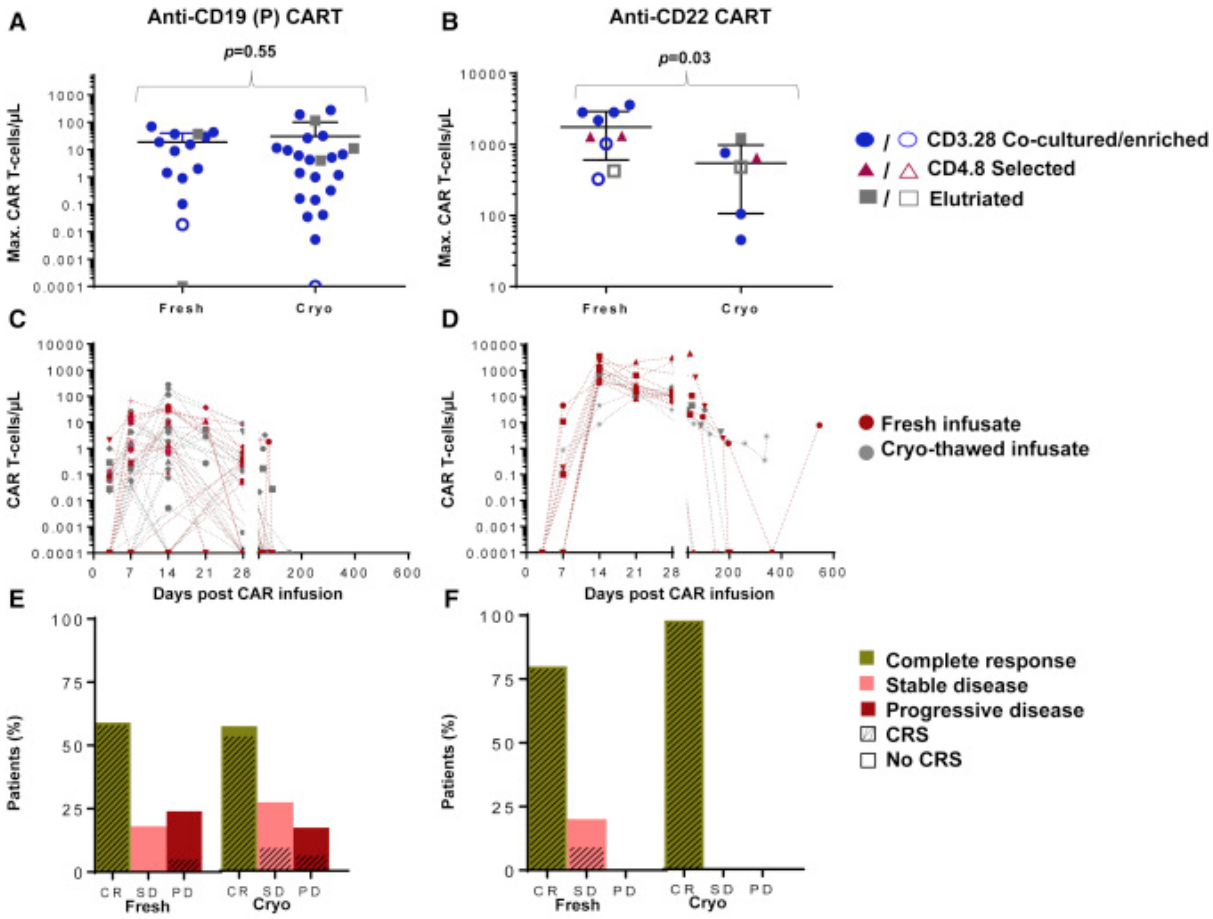
The most recent results for the cryopreserved formulation of OTL-200 were provided on pages 1006 to 1065 of Appendix A_22JAN21_Final_Tables_Figures_Listings.pdf submitted with the ERG clarification questions in January. Orchard notes that the ERG previously raised an issue around a perceived decline in ARSA CSF levels with the cryopreserved formulation at around 6 months, which was discussed briefly at the first HST committee meeting on 15th April 2021. Consequently, Orchard would like to provide further information within this document to help alleviate any remaining concerns.

It is recognised by clinical experts in MLD that CSF-ARSA levels, as with many CSF enzyme levels, fluctuate naturally, and this would be expected within the general population. This is one of the reasons why CSF levels are not used as a measure of response in clinical practice, as they do not corelate with clinical outcomes such as GMFM, GMFC or DQ. This pattern of ARSA fluctuation was also observed with the fresh formulation - of the 11 patients with ARSA

CSF measurements between Day 90 and Year 1 in the pivotal study, [redacted] had declines in their CSF-ARSA values. These declines were not associated with worsening of clinical outcomes. In fact, between Day 90 and 1 Year, [redacted] with available GMFM data saw increases in their GMFM score, while [redacted] All patients GMFC-MLD scores also stabilised in this time frame. These results indicate that the "apparent decline" in CSF-ARSA values observed in three of the patients did not translate into having any material clinical impact. Finally, EMA has assessed all the available data and raised no concerns with the use of the cryopreserved formulation, which provides several clear benefits to patients and their carers including: allowing them receive treatment and follow-up closer to home, in their own country, rather than have to travel to Milan to receive treatment. It also allows for additional quality control of the drug product prior to administration, and scheduling and optimisation of timing of conditioning and infusion for the patient and treatment site.

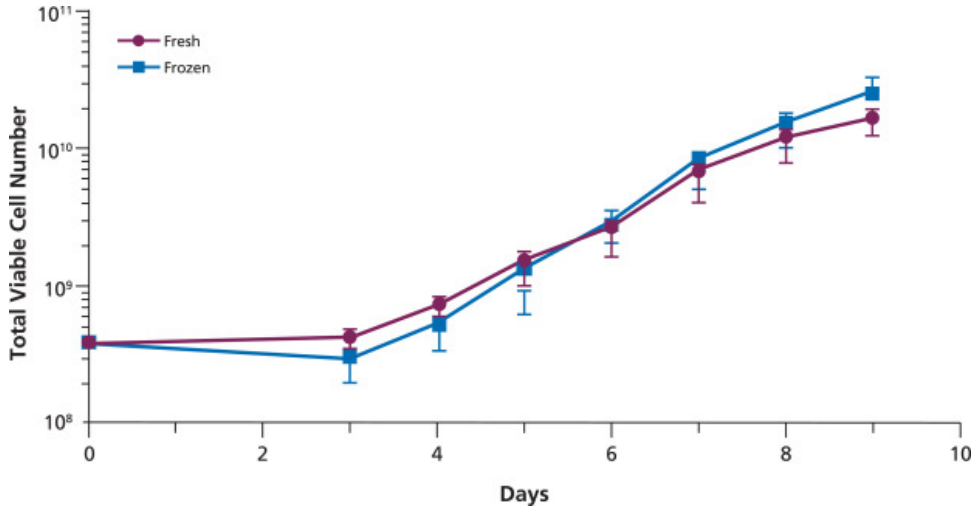
The clinical experts at the first NICE HST committee meeting on the 15th April 2021 stated that they would not expect to see any difference in clinical outcomes between the fresh and cryopreserved formulation of OTL-200 based on their experience with other cryopreserved cell therapies. To support this, Orchard has conducted a review of the literature to look at evidence for equivalence between the two types of formulation. The primary objective of a paper published by Panch et al in 2019, was to determine the impact of cryopreservation on chimeric antigen receptor T cells (CAR-Ts). In a subset of patients who received fresh or cryopreserved final products at a standard dose, the authors compared *in vivo* CAR-T levels, persistence over time, and clinical response. Results are shown in Figure 1 below.

Figure 1: Comparison of *In Vivo* Levels and Persistence of CARTs Infused Fresh or after Cryopreservation



As can be seen from the figure above, clinical response with the cryopreserved formulation was equivalent to the fresh formulation. Furthermore, a paper by Tyagarajan et al published in 2019 investigated the autologous cryopreserved leukapheresis cellular material for chimeric antigen receptor-T (CAR-T) cell manufacture. Leukapheresis is the process of cell harvest, and in this paper the authors compared the viability of both fresh and cryopreserved harvested cells for manufacture of the gene therapy product. This paper showed that utilising cryopreserved leukapheresis enabled the successful manufacture of an autologous CAR-T for use in over 50 centres in 12 different countries. Whilst it is cryopreservation at the leukapheresis stage, rather than end-product, this paper presented results from a separate comparability study to evaluate growth kinetics using fresh and cryopreserved leukapheresis - comparable cell growth kinetics were observed using both processes (Figure 2 below). The cryopreserved CAR-T gene therapies have both been approved by NICE (TA554 and TA559).

Figure 2: Evaluation viable cells for fresh and cryopreserved formulations



Moreover, cryopreservation is not exclusive to gene therapies, and is also a methodology used for the preservation of cord blood. The NHS Blood and Transplant information pages state that once the cord blood unit has been frozen, it will be stored until a patient requires it. Research has shown that units can be stored for 25 years or more and still be used successfully in a stem cell transplant.

Therefore, it can be concluded that the cryopreserved and fresh forms of OTL-200 are expected to be comparable in terms of clinical outcomes. In recent days, another HSC gene therapy for CAL-D has received recommendation for European Marketing Authorisation by the CHMP indicating that regulators are confident in the cryopreserved formulations.

2 Population – distribution of MLD variants with focus on ES EJ

2.1 Proportion of MLD variants

The company acknowledges the ERG's views that there are uncertainties in the distribution of patients across MLD subtypes and that, in the absence of an older affected sibling, the likelihood of diagnosing symptomatic early juvenile patients in time to be treated is challenging. The company also agrees with the ERG's views that the proposed ERG distributions are reasonable and make the best use of the limited available data. The company had considered a similar approach when developing the economic model, but ultimately decided to use a conservative approach by using the values sourced by the clinical experts as it had a higher proportion of ES-EJ patients (Experts: 35.6% vs. ERG14.9%).

Orchard considers that due to an increase in MLD disease awareness and improvements in diagnosis, along with the potential for an available treatment if OTL-200 is approved, the proportion of ES-EJ patients would reduce over time with nearly all patients eventually being pre-symptomatic at point of treatment. However, until such a time, it is important to note that ES-EJ patients still have the capacity to benefit with OTL-200 treatment especially if caught early with the possibility of stabilising at GMFC-MLD 0 or 1 with normal cognitive function allowing them to live a close to normal life, as shown by the clinical data and supported by the expert testimonials.

The company has therefore presented two scenarios with updated cost-effectiveness estimates (see Section 6), where scenario 1 uses the ERG base case for the distribution of MLD sub-types and scenario 2 uses the company's base case estimates.

2.2 Diagnosis of [redacted]

In relation to the proportion of likely ES-EJ patients that will be eligible for treatment with OTL-200, the ERG presented an analysis of baseline characteristics of the ES-EJ patients in the clinical trials in Appendix B of the Addendum report, which has resulted in a clarification question around the age at treatment and disease onset for two of the patients in this group – [redacted]. It is not clear the purpose of the analysis done by the ERG, nevertheless as these patients are ES-EJ patients who meet the licensed indication, the company believes their data should be included in the evaluation by NICE.

[redacted]

[redacted]

[redacted]

3. Response rates – some unstable partial responders have the potential to stabilise at GMFC 3 and 4 rather than have continued disease progression

In the Addendum report, the ERG notes that both the company and the ERG adopted a conservative approach in assuming that a proportion of OTL-200 treated patients will have continued disease progression albeit at a slower rate than natural history. However, clinical experts in fact consider this to be an overly pessimistic view and indicated that the majority, if not all patients, will stabilise. Orchard acknowledges that some patients previously assumed to progress, could stabilise at GMFC-MLD 3 or 4. The biological rationale as to why a small proportion of patients continue to decline is not fully understood. One hypothesis is that the damage in the brain is so widespread that the pace of cross-correction by the ARSA released by gene corrected stem cells in the brain is insufficient to prevent further cell damage, resulting in the appearance of continued loss of motor and other skills. However, it is also equally likely that over time the pace of cross-correction may catch up with the pace of disease progression, which would result in stabilisation.

In the Addendum report, the ERG model two scenarios where all stabilised partial responders stabilise at GMFC-MLD 4. Whilst the ERG acknowledges that this is not intended to represent a realistic scenario, Orchard would like to re-iterate that this is an implausible scenario reflected by the results which show Best supportive care (BSC) dominating OTL-200 (Scenario 2a and 2b). This is because of the following reasons:

- Whilst Orchard considers that it is clinically plausible that some patients may stabilise at GMFC-MLD 4, the company thinks it is implausible that all ES-EJ patients would stabilise at GMFC-MLD 4 as the data shows that once treatment effect is established (~ 6 months to ~ 2 years), these patients see a stabilisation across all relevant clinical outcomes (GMFC-MLD, GMFM, DQ) as well as disease biomarkers (ARSA, MRI and NCV) up until the last follow-up (which in some cases is up to 8 years in total). In addition, data from the updated analysis in ES-EJ patients show that long-term stabilisation tends to occur at GMFC-MLD 1, 2 and 3.

- Furthermore, whilst Orchard understands that the ERG conducted scenario 2a and 2b to illustrate the impact of ES-EJ patients stabilising with a very poor HRQoL, expert testimony elicited at the committee meeting and clinical evidence indicates that OTL-200 provides multi-systemic benefits (beyond GMFC-MLD) compared to natural history patients. As such, OTL-200 treated patients in GMFC-MLD 3 and above would have better quality of life than their NHx counterparts in the same GMFC-MLD score. This is reflected in the vastly improved DQ scores for OTL-200 treated patients in GMFC-MLD 3 and 4 as compared to natural history.

The updated data analysis in Appendix A provides evidence to illustrate these points.

4. Utility set to inform QALYs – exploration of alternative value sets

Feedback from patient group experts indicated that gene therapy treated patients have much better quality of life than natural history patients at the same GMFC-MLD score, with reductions in seizures, pain, improved cognitive function and improvements in feeding representing some of the benefits treated patients experience. In the original company base case, these quality-of-life benefits were indirectly captured through the differences in distribution of patients across the cognitive substates for OTL-200 treated patients vs natural history patients.

However in light of the ERG's concerns that the size of the cognitive utility decrement may be too high (despite the company presenting evidence showing these decrements were less than those reported for Alzheimer's patients with moderate (-0.42) and severe cognitive impairment (-0.57) relative to mild cognitively impairment), and would not be monotonic across the different GMFC scores, the company has presented two alternative scenarios, which it hopes alleviates these concerns whilst capturing the utility benefit associated with OTL-200 treatment.

The company reaffirms that based on feedback from clinical experts, MLD is considered to be more severe than other devastating conditions such as CLN 2 and SMA, as such the utility approaches detailed below are conservative. Furthermore, we have engaged leading experts in utility measurement who have conducted several utility exercises used for decision-making in HST appraisals and are members of the NICE methods group.

4.1 Alternative utility set 1 - regression analysis results for the rescaled utility set provided to NICE on 14th April 2021 based on the EQ-5D floor value for the UK

Orchard acknowledges that the approach used for the utility study deviated from the preferred approach for collection of utilities directly from patients or their caregivers using the EQ-5D instrument. The company believes this deviation is justified for the reasons mentioned below in Section 4.3. However, the company recognises NICE's concerns that accepting values below the EQ-5D-5L floor value of -0.594 would result in inconsistencies between appraisals which have used the EQ-5D-5L instrument and as such are bounded by this lower limit.

In the ERG Addendum report, the ERG noted a number of logical inconsistencies in the revised values for the utility set provided to them on the 14th April 2021. Inconsistencies (defined as when respondents assign values to different health states that may violate the logical order expected) between some of the health states is not surprising and would be expected given they are adjacent to each other. Indeed, a study in 2006 showed that when a representative sample of 309 Dutch adults were asked to value 17 EQ-5D health states by VAS and TTO, 65% had inconsistencies for VAS and 89% for TTO. The authors concluded the presence of these inconsistencies did not affect the estimated tariffs (Lammers et al 2006).

To address both NICE and the ERG's concerns, the company has rescaled all negative values obtained in the TTO exercise of the utility study for the juvenile states to fit within the range of 0 to -0.594 using a linear regression model (rescaled utility values presented in Table 1 below). For example, -1 now equates to -0.594 and -0.5 equates to -0.297. Using the regression model to calculate the mean TTO scores removes the inconsistencies mentioned by the ERG and is a recognised, and widely accepted approach. Please note the utility set provided on 14th April 2021 were rescaled utility values of the raw utilities obtained from the study. They were not based on a linear regression hence the very slight inconsistencies.

Table 1: Mean TTO scores for all juvenile MLD health states using the rescaled approach in the UK

Health States	TTO score
GMFC1 + normal cognition	XXX
GMFC2 + normal cognition	XXX
GMFC3 + normal cognition	XXX
GMFC4 + normal cognition	XXX
GMFC5 + normal cognition	XXX
GMFC6 + normal cognition	XXX
GMFC0 +moderate cognitive impact	XXX
GMFC1 +moderate cognitive impact	XXX
GMFC2 +moderate cognitive impact	XXX
GMFC3 +moderate cognitive impact	XXX
GMFC4 +moderate cognitive impact	XXX
GMFC5 +moderate cognitive impact	XXX
GMFC6 +moderate cognitive impact	XXX

GMFC0 + severe cognitive impact	XXX
GMFC1 + severe cognitive impact	XXX
GMFC2 + severe cognitive impact	XXX
GMFC3 + severe cognitive impact	XXX
GMFC4 + severe cognitive impact	XXX
GMFC5 + severe cognitive impact	XXX
GMFC6 + severe cognitive impact	XXX

The rescaled values now align very closely with CLN2 utilities used in HST12, which clinical experts have indicated is less severe than MLD.

ICERs for OTL-200 vs BSC using this rescaled utility set are provided in Section 6.

4.2 Alternative utility set 2 – incorporating a utility 'top-up' for the cognitive benefits based on CLN2 utility values used in HST12

Orchard considers that the utility values from the vignette study, or the rescaled utility values presented in 3.1 above, are robust and suitable for decision making purposes. As noted above, there is a distinct and separate HRQoL decrement associated with loss of cognitive capacity that is not captured by loss of motor skills. Furthermore, OTL-200 treated patients who are in GMFC-MLD score of 3 to 6 display additional treatment benefits beyond GMFC-MLD such as improvement in cognitive function allowing patients to continue to learn and/or retained communication, no swallowing/feeding problems, reduction in seizures, bowel & bladder problems, and improvements in vision.

However, the company recognises that the ERG still has concerns around the magnitude of the cognitive benefit. Consequently, Orchard has developed an alternative set of utility values to facilitate decision making. The company proposes to use the normal cognitive utility for each GMFC stage and include a utility 'top-up' for OTL-200 patients to reflect the improved cognitive function and other benefits (such as improvement in cognitive function allowing patients to continue to learn and/or retained communication, no swallowing/feeding problems, reduction in seizures, bowel & bladder problems, and improvements in vision) associated with treatment not mediated by GMFC-MLD.

The closest disease analogue to MLD is CLN2, with patients experiencing progressive loss of both motor and cognitive function over time. Disease stage in CLN2 is calculated by summing the motor score (1-3) and the language score (1-3), such that for example disease stage 4 equates to a 2 on the motor scale plus 2 on the language score; and disease progression increases with decreasing disease stage (Table 1, Gissen et al 2021).

Consequently, based on a recently published utility study in CLN2, the company has been able to estimate the cognitive decrement for patients with severe motor impairment (motor score of 1 = requires assistance to walk or can crawl only) as the CLN clinical rating score for disease stage 1 to 3 is calculated as severe motor + language score as follows 1+0, 1+1, 1+2. Orchard has assumed that a 2-point drop in language score i.e., a decline from 2-0 is equivalent to the severe cognitive impairment decrement reported in patients with MLD.

In the CLN2 utility study, a 2-point drop in language equated to a utility decrement of 0.276 (see Table 6, Gissen et al 2021). Therefore, the company has used this value (i.e., 0.276) as a proxy 'top-up' for 80% of OTL-200 treated patients who are in GMFC-MLD score of 3 to 6 to capture the additional treatment benefit beyond GMFC-MLD associated with treatment. The company has assumed that only 80% of OTL-200 treated patients will receive the 'top-up' because whilst the vast majority of patients treated with OTL-200 had sustained improvements in their cognitive function, 2 patients (1 LI and 1 ES-EJ) experienced a decline in cognitive function (see Appendix A).

ICERs for OTL-200 vs BSC using this alternative value set are presented in Section 6.

4.3 Company response to ERG's concerns regarding the company utility study

As previously mentioned in Section 4.1 above, Orchard considers that the original vignette study utility value set are appropriate for decision making, which was supported by both clinicians and patient groups at the first HST committee meeting on 15th April, 2021. The company acknowledges that the approach deviated from the preferred approach for collection of utilities directly from patients or their caregivers using the EQ-5D. However, this approach is not new and has been accepted by NICE in the past (for e.g. TA155 direct elicitation of utilities from the members of the public without a choice-based tool was accepted by NICE).

Furthermore, as stated in previous correspondence the vignette study was used for four main reasons: (1) EQ-5D is not a suitable tool, because it does not capture some of the key drivers of quality of life in MLD patients such as cognitive function, impact of seizure, lack of communication etc. (2) No other choice-based instruments are suitable. (3) Recent guidance from NICE (CHTE Methods Review: Health Related Quality of life Task and Finish group) recommends Vignettes as an alternative approach for obtaining utilities for health states. (4) Given the number of health states involved (24), and the limited number of MLD experts, it wasn't practically possible to do a TTO task with them, neither would it be methodologically appropriate given public preferences are required.

The vast majority of vignette approaches elicit utilities from members of the general population. In addition, the company enlisted the advice of several methodological leaders in utility measurement including members on the NICE task and Finish group when designing the study, as well as sense checking the values with different clinical and methodological experts once the study had been completed due to the large negative values.

However, as discussed in section 4.1, the company has adopted a pragmatic approach to address the ERG's concerns for not using the EQ-5D, by rescaling the original utility values to the floor value of the UK EQ-5D set (-0.594). The rescaled value set aligns with the published CLN2 utilities, a disease which is similar in severity, although not quite as severe as MLD. For example, the utility for the worst disease stage in CLN2 is -0.389 (Table 6, Gissen et al 2021), which is very similar to the worst health state in the rescaled MLD value set – where GMFC-MLD 6 with severe cognitive impairment has a utility score of [redacted].

5. Stabilisation

In the ERG Addendum report, the ERG discusses the permanence of the treatment effect and states that it represents a key uncertainty and driver of model outcomes. The committee has indicated it has a preference for setting the stabilisation parameter at an arbitrary 20 years rather than lifetime as a consequence of this uncertainty. Orchard acknowledges that data for OTL-200 does not yet exist beyond 10 years, however as outlined below there are a number of key considerations for the committee that the company considers support, at a minimum,

stabilisation for 30 - 50 years. As such, scenarios with 30 - 50 years and lifetime should be explored by the committee.

5.1 Mechanism of action of OTL-200

As originally presented in the company submission there are three distinct stages to the mechanism of action of OTL-200 which are explained in Table 2 and Figure 3 below:

Table 2: Three stage mechanism of action of OTL-200

	Stage 1: Peripheral Engraftment and reconstitution of bone marrow	Stage 2: Repopulation of the tissues and cross-correction	Stage 3: Long term
Process	**Engraftment:** Following myeloablation, the gene-corrected stem cells migrate to and engraft in the bone marrow. **Reconstitution**: Following engraftment reconstitution of the patient's haematopoietic and immune system occurs as evidenced by absolute neutrophil count (ANC) ≥500/μL.	**Repopulation:** Progenies of the gene corrected stem cells migrate to multiple tissues, including the brain, where they become resident and deliver ARSA enzyme. **Cross-correction:** ARSA secreted by gene-corrected cells is taken up by neighbouring neurons and oligodendrocytes providing cross-correction for enzyme-deficient cells. Depending on the level of cell damage present, it may take up to 24 months for the ARSA enzyme to breakdown already accumulated sulfatides and halt the inflammatory processes that causes cell damage.	The gene corrected stem cell progenies that have become resident in the brain compartment and other tissues are stably engrafted. Gene correction is maintained. These cells continue to durably produce and secrete ARSA enzyme, preventing further sulfatide accumulation and cell damage.
Duration	0 – 3 months	0 – 24 months	24 months onwards
Biological markers	PBMC ARSA and VCN	PBMC ARSA and VCN	Clinical outcomes
Therapeutic effect	**No overt impact on disease course is expected at this stage. However, lack of successful engraftment would result in treatment failure.**	**Treatment effect starts to become apparent. It may take up to 24 months for the full effect of the drug to become apparent.**	**Depending on the stage in the disease course that treatment took place, treatment would slow or stop disease progression. -CSF-ARSA levels may fluctuate as is**

			observed in normal population.

As Table 2 above highlights, autologous stem cells and progenitors are able cross the blood brain barrier and produce progeny with the corrected gene for ARSA production.

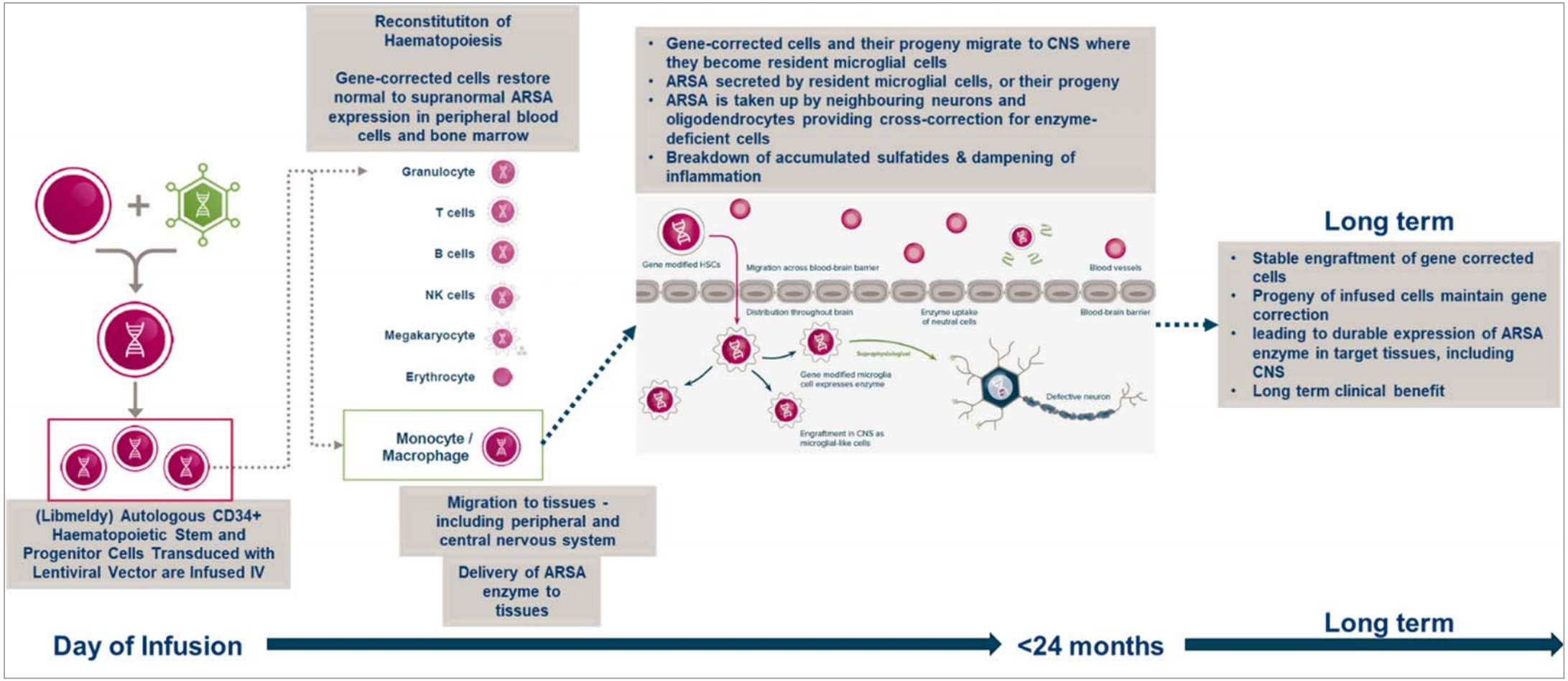
There is no evidence to support loss of engraftment or stabilisation based on the MoA of OTL-200 and available follow up data. This is further supported by 20-year efficacy data for another autologous gene therapy - Strimvelis (Section 5.3.1) and at least 30 years of stable engraftment using HSCT for Hurler's syndrome (Section 5.3.2). In addition, HSCT has been used for over 50 years to treat patients with several diseases and has shown to be effective in preventing disease progression[1]. Consequently, the committee's preferred stabilisation of 20 years is not supported by the available evidence and would significantly underestimate the benefit of OTL-200.

Furthermore, the assumption of potential life-long stabilisation aligns with what the leading UK clinical expert in transplant has reported (refer to section 5.3.2 for further details); and previous NICE appraisals of transplant therapies in other conditions have concluded (TA554 and TA559).

Of important note, traditional allogenic stem cell therapies carry the risk of graft failure due to immunological rejection of the transplant. Orchard would like to point out, that the reason why most HSCT grafts fail is due to the body's immunologic rejection after time of a recognised foreign body, and this would not be the case with an autologous gene therapy. Hence whilst HSCT convenes long-term durability in a number of diseases, engraftment results with OTL-200 would be expected to be superior to allogeneic HSCT.

[1] The first clinical study of allogeneic HSCT was initiated in 1969 by Dr Thomas to treat patients with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). Of the 1st 100 patients treated with HSCT, the authors reported a cure rate of 13 percent who were alive and without disease after HSCT. Thomas ED, Buckner CD, Banaji M, et al. One hundred patients with acute leukaemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood. 1977;49:511–33

Figure 3: Schematic of the MoA of OTL-200



* ~8 years of follow-up

5.2 OTL-200 results for multiple outcome measures including biomarkers

In the ERG Addendum report it states, “the ERG re-emphasises that the presented data is not wholly supportive of the concept of permanent stabilisation… there is evidence of continued decline in relevant biomarkers…” Orchard would like to re-iterate that for full responders, broad stabilisation or improvement is demonstrated across important clinical outcomes and relevant disease markers (see Figure 4 below).

Furthermore, as discussed in Section 5.1 above, there is a degree of variability amongst patients as to when the drug will have its full affect i.e., it is dependent on the amount of sulfatide accumulation at time of treatment and how long it takes the newly restored ARSA enzyme to break down this accumulation. Consequently, for partial responders there will be some level of treatment effect during the second stage, enough to halt or slow down disease depending on the level of damage already present, which is why in some patients there is an initial decline in clinical outcomes post gene therapy up to 2 years, but then once sulfatide accumulation has been broken down, they remain stable at that state across multiple outcome measures (see Figure 5 below). For patients classified as unstable partial responders, there is continued progression in multiple outcome measures of disease, exemplified in Figure 6 below.

Whilst the exact reason why these patients progress is not known, it is possible that the damage in the brain is so widespread that the pace of cross-correction by the ARSA released by gene corrected stem cells in the brain is insufficient to prevent further cell damage, resulting in the appearance of continued loss of motor and other skills. However, it is also equally likely that overtime the pace of cross-correction may catch up with the pace of disease progression, which would result in stabilisation

Figure 4: Exemplar of a full responder. All clinical outcome measures (GMFC-MLD, GMFM, Development Quotient performance [DQp]) and biological or disease markers (MRI, ARSA-PBMC, ARSA-CSF, Nerve Conduction Velocity [NCV]) are either improving or show broad stabilisation throughout follow-up period. (December 2019 Data Cut).

Figure 5: Exemplar of a stable partial responder. After 2 years, all clinical outcome measures (GMFC, GMFM, DQp) and biological or disease markers (MRI, ARSA-PBMC, ARSA-CSF, NCV) are either improving or show broad stabilisation throughout follow-up period. (December 2019 Data Cut).

Figure 6: Exemplar of an unstable partial responder. Some clinical outcome measures (GMFC, GMFM, DQp) and biological or disease markers (MRI, ARSA-PBMC, ARSA-CSF, NCV) are worsening over the follow-up period. (December 2019 Data Cut).

These data are supported by feedback from the leading HSCT specialist at Central Manchester University Hospitals NHS Foundation trust discussed in 5.3.2 below, who indicated that early engraftment leads to good biochemical, clinical and disease outcomes for the patient and if a patient is going to fail with transplant, they will fail early, which gives confidence in the updated data analysis showing consistent response rates over a longer period of time.

5.3 Long-term stabilisation data for Strimvelis and other stem cell therapies

5.3.1 Long term data for Strimvelis

Strimvelis is an autologous gene therapy for the treatment of ADA-SCID. In the most recent periodic benefit risk evaluation report (PBRER) for Strimvelis submitted to EMA on 26 January 2021, a range of 2 to 20 years of effectiveness data were presented (depending on the time the patient was treated). The second part of the long-term follow-up study completed in June 2019 and the final CSR was submitted to EMA on 20 December 2019. The key findings from this study showed that Strimvelis led to 100% long-term survival for subjects in the study. The majority of subjects demonstrated evidence of engrafted gene-modified cells, sustained increases in functional gene-modified lymphocytes, maintenance of a robust immune reconstitution, significantly fewer severe infections over time and continued physical growth.

5.3.1 Clinical Expert experience of using HSCT for treatment of Hurler syndrome

As discussed in Section 5.1, the mechanism of action of OTL-200 enables cross-correction and production of progeny cells with the corrected gene which leads to long-term stabilisation of response. Given there are not data beyond 8 years for OTL-200, Orchard considers it relevant to look at data from some of the first patients transplanted with stem cells in the UK.

Orchard sought the expert opinion on long-term stabilisation gene therapies from the UK leading transplant specialist in lysosomal storage diseases. The expert indicated that stable vector copy number (VCN) and polyclonality is the analogue of stable donor cell engraftment and chimerism in allogenic transplantation. In the allogenic setting, stable initial engraftment is predictive of stable long-term engraftment, which then translates to stable biochemical correction, clinical outcomes, and survival. The observation of stable VCN and polyclonality for OTL-200 in his opinion indicates that the autologous cells will continue to remain engrafted and correlate with long term clinical and disease response.

The expert also confirmed that patients with Hurler's syndrome who received transplant as children, and are now in their 20s and 30s, have maintained clinical response without seeing waning of effect. In fact, for some of the earliest metabolic patients who were transplanted, they can now provide 30 years' worth and still counting of follow-up demonstrating long-term stabilisation.

Data from Lum et al 2017 show that there is now a survival plateau in Hurler's syndrome patients for what was once a fatal illness, due to successful HSCT. Whilst outcomes in HSCT for MPS1H may not be perfect and there is scope for improvement, the survival plateau and long-term maintenance of engraftment provides further evidence of long-term disease stabilisation. Figure 7 below illustrates the point made above that if graft failure is to occur it occurs early and then there is long term stabilisation.

Figure 7: Survival probability of Hurler Syndrome patients treated with HSCT

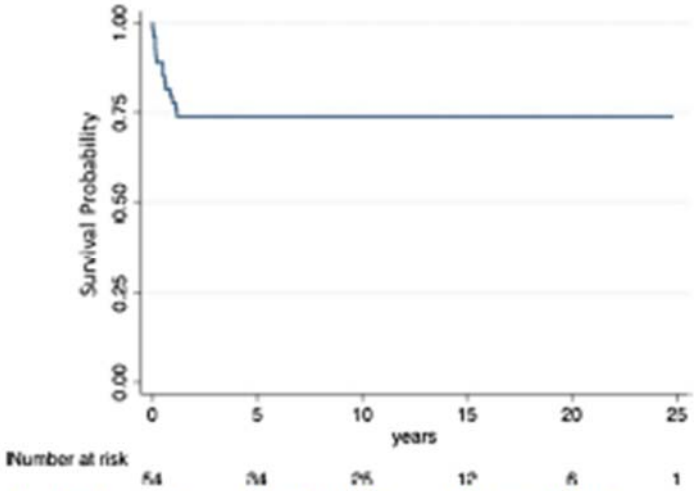


Fig. 2 The overall survival of 54 children with HS after HSCT

Orchard recognises that based on the recent evaluation of other gene therapies, the committee may have had some reservations about the durability of effect. However, given the unique modality of ex vivo gene therapies, these reservations do not apply to OTL-200 for the following reasons. The MoA of OTL-200 is broadly based on the principle of allogenic haematopoietic stem cell transplants (HSCT) which have shown ongoing durability of effect for metabolic patients beyond 30 years. OTL-200 leverages the same HSCT platform to be able to self-propagate and renew. This is supported by experienced UK clinical experts in HSCT procedures. In addition, the MoA of OTL-200 enables the direct integration of the corrected gene into the genome unlike in vivo gene therapies. HSCT has been used for over 50 years to treat patients with several diseases and has shown to be effective in preventing disease progression in these patients.

Therefore, to re-iterate, Orchard considers that there is evidence in transplant for other disease areas, relevant to this therapy, that show a 20-year stabilisation period is not appropriate for decision making in this instance. As such, scenarios with 30 years - as a minimum, 50 years, and lifetime should be explored by the committee.

5.4 Additional benefits of gene therapies over allogenic HSCT

As mentioned in 5.3 above, allogenic HSCT has had some success in the treatment of a number of diseases, but it is not without it's limitations in terms of efficacy and safety e.g. graft failure and graft vs. host disease. Ex-vivo gene therapies like OTL-200 leverage the successful platform of HSCT, but without the immunological complications and are able to provide supraphysiological levels of the deficient enzyme which potentially enables quicker intervention in the disease course.

5.5 Addressing the ERGs concerns regarding CSF- ARSA and gene silencing as factors for long-term stabilisation

5.5.1 CSF-ARSA

On page 5 of the Addendum report, the ERG state, "The declining levels of CSF ARSA activity observed in several late infantile and pre-symptomatic early juvenile patients are of specific concern". This was discussed at the committee meeting on 15th April and both clinical experts

stated that they do not measure CSF ARSA levels in clinical practice because enzyme levels naturally fluctuate, and they do not corelate with clinical outcomes such as GMFM, GMFC-MLD or DQ.

However, given this issue has been raised again in the ERG Addendum report, Orchard would like to re-iterate that it is normal, physiologically, for CSF enzyme levels to fluctuate between samples. The test is still valid and reliable, however fluctuations are typical and to be anticipated. No correlation has been observed between levels of ARSA and clinical outcomes.

For example, in the pivotal study, at year 2; 7 patients had CSF-ARSA values ≤0.71nmol/mg/hr. No relationship between ARSA levels and GMFM was observed, indeed Table 3 below illustrates this point.

Table 3: CSF-ARSA and GMFM scores at 2 years post gene therapy

Patient	MLD phenotype	GMFM score	CSF-ARSA
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

It is therefore important to consider enzymatic function at the cellular level, where ARSA is acting to break down sulfatides. CSF is an extracellular fluid and values do not reflect the intracellular enzymatic activity, in the same way that plasma levels of enzymes do not reflect what is in the cells. This misalignment is recognised in the MLD clinical community, hence why recent clinical trials in MLD are looking into CSF sulfatide levels as a possible better marker (Dali et al 2020, Molecular Genetics and Metabolism Volume 131, Pages 235-244).

As mentioned in previous correspondence on this matter, the most important aspect to measure efficacy is to observe clinical effects, rather than proxies, and here the data show robust and durable clinical benefits for patients. It is important to remember that CSF-ARSA was an exploratory outcome measure which has successfully demonstrated an important component of the mechanism of action of OTL-200 – the ability for corrected cells to cross the blood brain barrier and engraft in the brain, producing functional ARSA enzyme and resulting in clinically meaningful outcomes for patients. This is particularly relevant for the cognitive benefit observed in OTL-200 patients.

5.5.2 Gene silencing – preclinical mouse data

In the ERG report it discussed the fact that the EMA had raised the issue of gene silencing as a concern for long-term stabilisation, based solely on the poor VCN-ARSA activity correlation observed in pre-clinical studies involving mice. This poor correlation was attributed to potential gene silencing of the integrated lentiviral (LV) cassettes (Capotondo et al 2007).

However, it is important to clarify that a positive VCN-ARSA activity correlation was present in patients in the clinical studies, and the concern the EMA had is based on the potential possibility of gene silencing occurring in patients.

There are a number of key points to consider regarding this potential possibility that Orchard hopes will alleviate the committee's concerns:

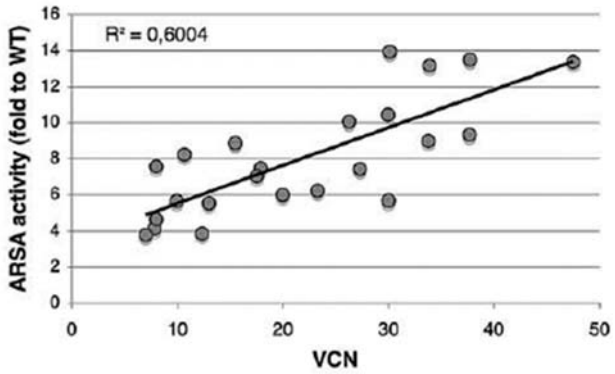
- The purpose of the non-clinical study mentioned above was to study the safety of supraphysiological levels of ARSA activity. Hence the mice used in these studies were specifically designed (Transgenic mice) to overexpress ARSA enzyme up to 15-fold above the normal range and carrying multiple copies of the lentiviral vectors (Vector copy number VCN) in their genome. This is much higher than what is observed in treated patients (VCN target of ≤4).

- Whilst characterization of these mice demonstrated the safety of ARSA overexpression in both the Hematopoietic Stem and Progenitor cells (HSPCs) and neurons, it is worth highlighting the poor VCN-ARSA activity correlation was observed from a sub-set of the transgenic mice that had consistently high ARSA (≥ 5 fold above normal values) and VCN (≥ 5) values. The authors attributed the poor correlation to potential silencing of some of the LV.

- It is worth noting (as can be seen in the figure below) that even at the high VCN levels, the ARSA activity was still at supraphysiological levels and continues to increase (albeit at a slower rate) as VCN levels increased.

- The VCN in PBMC for treated patients was much lower: At 2 years, the mean VCN in the clinical trial was 0.760 (range is 0.1 to 4.630) per cell and remained stable after then.

Figure 8: ARSA activity of PBMCs and VCN in ARSA Transgenic Mice (Capotondo et al 2007)



Therefore, Orchard considers that the potential gene silencing observed in the transgenic mice was because the levels of ARSA were so extraordinarily high that as a feedback mechanism to control this, potentially some of the ARSA encoded genes were silenced in an attempt to normalise levels. This would not be the case in humans, where reported levels were at least 5-fold lower than seen in the mice, and still considered supraphysiological.

6. ICERs from the scenario analyses using the ERG corrected company model

In light of the points mentioned above, Orchard presents the following alternative scenarios which the company hopes support decision making and addresses the uncertainties identified by the committee in the original base case presented in the company submission. These alternative scenarios are based on the ERG alternative base case presented in the ERG Addendum report with changes to the utility set, response rates, progression modifiers and stabilisation included. A list of the changes made to the ERG alternative base case are summarised in Table 3 below:

Table 4: Summary of key changes the company has made to the alternative ERG base case

Parameter	Alternative Company Base Case	Comments
Utility Score	Rescaled utility (normal cognition) + top-up for OTL-200 patients in GMFC 3 and above	▪ Treatment has been shown to impact other disease beyond motor function even for the same GMFC score, which has been confirmed by patient experts. ▪ Approach addresses concerns of utility face validity and level of cognitive decrement.
Disease stabilisation	50 years	▪ Whilst we believe response would be durable and lifelong, we recognise that HSCT only became a viable treatment option 50 years ago, as such outcomes beyond 50 years are unknown. [2] 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)	▪ Set to [redacted] all values [redacted] Use calculated progression modifier for ES-EJ patients	▪ Clinically implausible that treatment would accelerate disease progression ▪ PS modifiers inappropriate for ES-EJ patients given different probabilities of stabilisation.
Response rate ▪ **PS-EJ: 75% full responders** ▪ **ES-EJ:** o **20% - GMFC 1** o **20% - GMFC 3** o **20% - GMFC 4**	Based on updated data (Dec 2019 data cut)	▪ Recalculated base case using updated data (~5 year follow-up) for PS-EJ and ES-EJ only, given we had complete data for all patients. ▪ Assumed all unstable patients stabilise at 3 or 4.
Subgroup distribution		▪ ERG Base Case
Discount rate	1.5% and 3.5%	▪ Majority of PS-LI (72%) and PS-EJ (75%) stabilise at GMFC 0 to 1 and retain normal cognitive function (high level of quality of life)

Tables 5 and 6 presents the results of these additional scenario analysis considering the assumptions discussed above. Further scenario analyses showing the impact of each of the changes on the alternative company base case are also shown. All presented scenarios include the updated PAS price [redacted] available for OTL-200, which represents a reduction of [redacted] on the list price and an additional [redacted] less than the previously agreed PAS price.

[2] Henig and Zuckerman Hematopoietic Stem Cell Transplantation – 50 years of evolution and future perspectives. Rambam Maimonides Med J. 2014 Oct; 5(4):e0028

Table 5: Company Alternative Scenario Analysis (3.5% discount rate) – unstable partial responders progress – regression utilities

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
Alternative Company Base Case																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 1: Proportion of ES-EJ as per original company assumptions																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 2: Lifetime disease stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 3: 30 years disease stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 4: Original utility set																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 5: Unstable partial responders stabilise at GMFC 3 and 4																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 6: Rescaled utility set – no top up / adjustment																
BSC	[redacted]															

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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Company Alternative Scenario Analysis (1.5% discount rate) – unstable partial responders progress

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
Alternative 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: Proportion of ES-EJ as per original company assumptions																
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: 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 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: Original utility set																
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: Unstable partial responders stabilise at GMFC 3 and 4																

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]	[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: Rescaled utility set – no top up / adjustment																
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]

Appendix A

Given the short timeline for this response, Orchard has prioritised the key clinical outcomes and disease biomarkers in the updated data analysis. The outputs are presented as figures for individual patients where possible and are contained in a separate pdf. file submitted alongside this response document.

Due to the short time frame to compile this document, it hasn't been possible to generate outputs with patient listings in an analysable format, which the company understands would have been the ERG's preference.

Please note that all the data included in Appendix A are commercial in confidence.

Appendix B

Table B1: Estimation of progression modifier for ES-EJ (based on updated analysis using December 2019 data cut) n = 5 patients

Patient Identifier	Residence Time in Months[a]	
	GMFC 1 – 2	GMFC 2 - 3
MLD08	[redacted]	[redacted]
MLD13		
MLD14		
MLD17		
MLDCO2		
Average		
BSC (from model)		
Progression modifier		

[a] Estimated directly from individual patient GMFC Panel Plots in Appendix B
N.R. indicates patient has not yet reached GMFC 2 or 3. Patient assumed to have stabilised
N.A. patient only had one data point at GMFC 1, so wasn't possible to estimate residence time

Table B2: Response rate categorisation based on December 2019 data cut (n = 17). Patients were assumed to stabilise at GMFC 0 (full responders) or GMFC 1 – 4 (partial responder – stabilisers), if their clinical outcome parameters (GMFC, GMFM, DQ performance) and disease or biological markers (MRI, ARSA PBMC) had all shown evidence of broad stabilisation or continued improvement as at the last follow-up point (See Appendix A for individual patient data)

	Full responders	Partial responder -stabilisers				Partial responder - unstabilisers
		GMFC 1	GMFC 2	GMFC 3	GMFC 4	
Pre-symptomatic Late infantile (n=8)[a]	[redacted]		[redacted]			[redacted]
Pre-symptomatic Early Juvenile (n =4)[b]	[redacted]					[redacted]
Early symptomatic Early Juvenile (n =5)		[redacted]		[redacted]	[redacted]	[redacted]

[a] December 2019 data cut was for the pivotal study (201222) and CO2 (CUP 207394) studies which had in total 21 patients. [redacted]

OTL-200 for treating metachromatic leukodystrophy [ID1666]

ERG commentary on the updated model and additional evidence submitted

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Date completed	27/05/2021

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

Table of Contents

Table of Tables

Table of Figures

1 OVERVIEW

The Evidence Review Group (ERG) was requested by NICE to review and critique the additional evidence submitted by the company following the first committee meeting. Due to the limited resource available, the additional work undertaken by the ERG does not accord with the procedures and templates applied to the original submission. Instead, the ERG presents a critique of issues most likely to impact on the ICER and NICE decision making. Subsidiary issues raised by the company are noted in this report, but are not explored fully in the critique.

The main points raised in the company's response focus on the following four main issues:

1. A revised patient access scheme discount.
2. A new data cut (dated May 2021) which provides approximately 2 years of additional data on outcomes for 17 patients. This new data cut is used to update several parameters in the economic analysis, including those relating to treatment response which is a driver of cost-effectiveness.
3. The utilities set used in the model, for which a revised utility set is presented as well as additional evidence supporting quality of life benefits generated from treatment with OTL-200.
4. Uncertainties regarding stabilisation and durability of modelled treatment effects, for which new additional evidence is presented as well as additional scenario analysis.

The subsidiary issues raised by the company included:

1. The equivalence of cryopreserved and fresh formulation of OTL-200.
2. The distribution of patients across the three modelled groups: pre-symptomatic late infantile, pre-symptomatic early juvenile, and symptomatic juvenile.
3. The diagnosis and eligibility of patients [redacted] and [redacted].
4. Adjustments made to progression modifiers applied in the ES-EJ group, which are updated to reflect evidence from the new data cut.

2 UPDATED PATIENT ACCESS SCHEME (PAS)

The company has proposed a revised PAS which is now incorporated into a revised base-case. The PAS consists of a simple discount of [redacted] off the list price of OTL-200. This is an increase from the original PAS of [redacted].

With the revised PAS, OTL-200 is now priced at [redacted] (list price £ 2,875,000) per administration. The ERG has checked the revised economic model and is satisfied that the revised PAS has been correctly implemented by the company.

3 UPDATED DATA

The company supplied new data for the primary trial of OTL-200. This was in the form of figures of outcome data for each patient. No statistical analysis of these data was provided, and given the format of the data, the ERG was unable to statistically analyse these new data. Instead, the ERG has examined the data for each patient and summarised the changes in key outcomes (GMFC-MLD, GMFM, DQ and ARSA activity in CSF) since our original report. This summary is supplied as a separate spreadsheet, to preserve patient confidentiality.

The ERG notes the following key issues with the new data:

1. Several patients have experienced a decline in GMFC-MLD outcomes since the last data cut. Specifically, we note that [redacted] LI patients, [redacted] PS-EJ patients, and [redacted] ES-EJ patients have declined by one or more GMFC-MLD levels compared with the previous 2019 data cut. Declines in GMFC-MLD are matched by similar declines in GMFM.
2. Importantly, the updated data cut indicates that patients may stabilise for 2-3 years before experiencing a further decline in GMFC-MLD scores. See, for example, patients [redacted] (Appendix A P60) and [redacted] (Appendix A P66). The progression of patient [redacted] from GMFC-MLD 4 to GMFC-MLD 5 also indicates a continued pattern of decline. This casts doubt on stabilisation assumptions made and more broadly increases the burden of proof required to establish stability in specific patients.
3. Cognitive function (measured by DQ) remains good for most patients. Only [redacted] patients ([redacted] LI and [redacted] ES-EJ) have experienced clear cognitive decline. Interpretation of DQ data is complicated by the high within-patient variability over time.
4. ARSA activity in CSF shows continued decline in most patients. For [redacted] LI patients, [redacted] EJ-PS patients and [redacted] EJ-ES patients ARSA levels are near or below the minimum level for healthy adults (0.31 nmol/mg/h) and below the 0.71nmol/mg/h level which the EMA said may be indicative for treatment effect in LI patients (P62 of EPAR). Given the general decline in motor function described above, the ERG reiterates its concern that these declining ARSA levels may indicate declining treatment effectiveness in the longer term.

3.1 Revisions to modelled response rate

Section 1.2 of the company response outlines revisions to the response inputs based on the new May 2021 data cut. These revisions are limited to the PS-EJ and ES-EJ cohorts. Response rates used in the PS-LI group were not updated to reflect the new data because data were available for only 8 of the 15 patients in this group.

The ERG addendum prepared following the 1st committee meeting explored an alternative conceptualisation of the response categories. These consider alternative assumptions in which all partial responders stabilise and the unstable partial responder category is no longer used. Given the evidence provided by the new data cut, it is the ERG's view that this alternative conceptualisation is no longer supported by the data. The new data suggest a continuing pattern of decline in many partial responders, with far fewer patients achieving long-term stabilisation of disease symptoms. Furthermore, evidence from patient [redacted] suggests that this progression will not abate as patients reach GMFC-MLD 4. The ERG consequently considers that the original model structure and approach adopted in the alternative company base case is most likely to reflect the pattern of response observed in patients treated with OTL-200.

The ERG also concerned about the company's approach to updating the classification of patients into the three response categories. Specifically, it is unclear what decision rules have been adopted by the company in their revised classification of patients and specifically how this approach deviates from the decision rules proposed by the ERG. The classification of patients also appears inconsistent with previous analyses presented by the company. In this regard, the ERG notes the following inconsistencies in the company's approach:

- PS-LI group
    - Patient [redacted] remains classified as full-responder despite declining to GMFC-MLD 1.
    - Patients [redacted] and [redacted] have been included in the analysis of response despite having less than 12 months follow up. This is inconsistent with the ERG base-case and represents a pessimistic interpretation of the data as both patients are classified as unstable partial responders.
- PS-EJ group
    - Patient [redacted] has been removed from the sample. This patient died shortly after treatment and has previously been classified by both the company and ERG as an unstable partial responder.
- ES-EJ group
    - Patient [redacted] and [redacted] have been classified as stable partial responders despite experiencing a further decline in GMFC-MLD. This contradicts the classification of patient [redacted] who had previously been classified as a stable partial responder by both the company and ERG and is now classified as unstable reflecting the further decline in GMFC-MLD.
    - Patient [redacted] has be re-classified as stabilised partial responder. This patient had previously be classified as unstable by both the company and ERG.

- Patient [redacted] has been classified as a stable partial responder. This is consistent with the company's previous classification, but inconsistent with the ERG.
- Patient [redacted] has been removed from the data set. The company had previously argued this patient should be removed as they consider that would not be eligible for treatment.

Table 1 below summarises the response rates and how these have evolved from the previous iterations of the model. Individual assessment for each patient are also presented in Appendix A for transparency. The presented response rates include an updated assessment of response carried out by the ERG based on the previously developed criteria. These require: i) that full responders remain in GMFC-MLD 0 throughout follow up and to have at least 12 months follow up, and ii) that patients may only be classified as stabilised partial responders if declines in GMFC-MLD scores occur within 12 months of treatment.

Table 1 Response classification

	Original company base-case	**Revised company base-case**	**Original ERG base-case**	**Revised ERG base-case**
Pre-symptomatic late infantile	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])
Pre-symptomatic early juvenile	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])
Early-symptomatic early juvenile	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])	Full responders ([redacted]) Stable partial ([redacted]) Unstable partial ([redacted])

3.2 Revisions to distribution of stabilisation health states

As well as updating the response rates used in the model, the company also updated the distribution of GMFC-MLD health states over which patients stabilise. This update only impacts the ES-EJ group as no changes are made to the distributions used in the PS-LI or PS-EJ groups. This is appropriate as the new data cut does not imply any changes are necessary. The ERG considers this update to be broadly reasonable as it aligns with the current observed data. However, as noted previously, this approach assumes that no further progression will occur. This may not be reasonable given the limited follow-up and evidence of declining GMFC-MLD scores in patients following several years of apparent stability. The small numbers of patients also mean that the assumed distribution is unlikely to be representative of reality. Currently, [redacted] of patients are assumed to stabilise in GMFC-MLD 1 and [redacted] in GMFC-MLD 4. This is unrealistic as it is expected that patients will be distributed across the range (1 to 4) of GMFC-MLD health states. It is important to note that these assumptions do not

impact the ERG revised base case presented below. This is because all ES-EJ patients are considered unstable partial responders using the ERG's decision rules. Further analysis of these assumptions is therefore not implemented.

4 UTILITIES AND HRQOL

4.1 Alternative utility set 1 – regression analysis results for the rescaled utility set provided to NICE on 14th April 2021 based on the EQ-5D floor value for the UK

The linear regression exercise undertaken in the rescaled utility set appears to have resolved the issue of the external validity of the more extreme health state utilities. However, as negative values were rescaled into positive values, the LT-/TTO dichotomy of worse-than-death vs better than death has been broken. The values presented in Table 1 of the addendum response appear to match more closely those implemented in HST12. The company believes this value set to be conservative, given their position on the relative severities of CLN2 and MLD. However, the ERG notes that the most severe rescaled utility for MLD is now [redacted], compared to -0.389 as a worst utility in CLN2.

Furthermore, worse than death values in patients without cognitive impairment have now been removed, as the whole value set has been shifted upwards. This does not necessarily reflect the preferences of the TTO exercise participants, who explicitly chose to rate these health states as worse than death. The large independent effect of cognitive impairment also remains in this utility set.

The ERG's concerns regarding the magnitude of the decrements applied to patients with cognitive impairment remain. It also remains uncertain whether treated patients will be spared cognitive decline as their motor skills deteriorate, despite evidence suggestive of decline in patients treated with OTL-200. It is therefore not the ERG's preference to model utilities in this way. The ERG prefers the value set which preserves the worse than death health states in those with preserved cognitive function as rated by the public in the TTO exercise, and so we retain the original ERG value set in the preferred base-case.

However, the ERG considers this alternative utility set an acceptable compromise if the cognitive decrements are to remain, in that the most extreme values are brought more into line with the UK EQ-5D floor, and other comparable disease areas. This is therefore presented as a scenario on the updated ERG base-case.

4.2 Alternative utility set 2 – incorporating a utility 'top-up' for the cognitive benefits based on CLN2 utility values used in HST12

While the company describe this as an 'alternative' utility set, and that the rescaled utilities described in 4.1 above are robust and suitable for decision-making purposes, in their updated base-case they implemented a 'top up' to the utilities of patients treated with OTL-200.

This utility set appears to be an attempt to artificially improve the outlook for patients who stabilise at later stages of the disease, given the likelihood of this scenario based on the two years of additional data. This has a very significant impact upon the ICER, reducing it by around £153,000 for ESEJ patients, £5,500 for PSEJ, and £9,500 for PSLI.

This utility set is based on the assumption that treated patients will have very significant additional benefits of treatment beyond those hitherto raised. The company states that those with GMFC scores of 3-6 will have no swallowing/feeding problems, retained communication, reduction in seizures, improvements in vision, and improvements in bowel/bladder problems. The magnitude of this benefit varies (between 0 and 0.5), but is just large enough to ensure no utilities are worse than death for treated patients. The 'top-up' utilities are compared with the re-scaled set in Table 2.

Table 2: Company's alternative utility sets

Health States	Rescaled TTO utilities	Company base-case 'top up' set (OTL-200 treated patients)	'Top up' value in treated patients
GMFC1 + normal cognition	[redacted]	0.90	0
GMFC2 + normal cognition	[redacted]	0.82	0.01
GMFC3 + normal cognition	[redacted]	0.71	0.23
GMFC4 + normal cognition	[redacted]	0.40	0.36
GMFC5 + normal cognition	[redacted]	0.33	0.28
GMFC6 + normal cognition	[redacted]	0.29	0.28
GMFC0 +moderate cognitive impact	[redacted]	Gen. pop.	0.20
GMFC1 +moderate cognitive impact	[redacted]	0.90	0.25
GMFC2 +moderate cognitive impact	[redacted]	0.82	0.25
GMFC3 +moderate cognitive impact	[redacted]	0.43	0.25
GMFC4 +moderate cognitive impact	[redacted]	0.12	0.25
GMFC5 +moderate cognitive impact	[redacted]	0.05	0.25
GMFC6 +moderate cognitive impact	[redacted]	0.01	0.27
GMFC0 + severe cognitive impact	[redacted]	Gen. pop.	0.48
GMFC1 + severe cognitive impact	[redacted]	0.90	0.48
GMFC2 + severe cognitive impact	[redacted]	0.82	0.48
GMFC3 + severe cognitive impact	[redacted]	0.43	0.48
GMFC4 + severe cognitive impact	[redacted]	0.12	0.48

GMFC5 + severe cognitive impact	[redacted]	0.05	0.48
GMFC6 + severe cognitive impact	[redacted]	0.01	0.50

The company have provided no evidence in support of this additional level of symptom control associated with OTL-200. While it is possible that some of the stated benefits may have been anecdotally observed in some patients, it is clearly inappropriate to assume all treated patients will receive these benefits. It is also inappropriate to attribute an additive and arbitrary increase in utility for each, which implies that any purported resolution of the above symptoms is as important as a loss of motor function. These utilities represent a major departure from prior discussions and assumptions underpinning the previous utility sets and cannot be considered suitable for decision making.

5 STABILISATION

The ERG noted above (Section 3) our concerns about lack of stabilisation in motor function in many patients, given continued decline in GMFC-MLD scores, with many patients experiencing decline following long periods (2-3 years) of apparent stability as of the latest data-cut. It is therefore currently unclear whether any patients will experience long-term stabilisation, or how much impairment they will have at stabilisation.

The data suggest that long-term follow up is required to demonstrate stabilisation, with at least 3 years with no decline in GMFC-MLD being the minimum requirement. Only one patient who has experience decline in motor function currently fulfils that criterion ([redacted]). The ERG further notes the decline in GMFC-MLD observed in patient [redacted] after a period of approximately 7 years stability and no previous evidence of decline. This suggests that amongst some patients, decline in function may occur over very long periods (decades) and would not readily be observed even with the additional data the company have been able to provide.

The company provided some further commentary on stabilisation, with reference to other conditions. The ERG is unable, in the available time, to comment on other conditions, as these are outside our experience. However, we consider that assessments of stabilisation should be based on the evidence for OTL-200, and cannot be reliably inferred from technologies used in other conditions. Given the latest evidence for OTL-200 suggests patients lose stability and/or continue to decline, it is inappropriate to assume lifetime or very long-term stabilisation based upon equivalence with other technologies which have demonstrated long-term effectiveness.

Further, as already noted (see Section 3) the ERG remains concerned about declining ARSA activity in CSF. The new data have only increased this concern, as ASRA activity has continued to decline in many patients. We reproduce below (Figure 1) the summary plot of ARSA activity in CSF provided by the company in the new data appendix. We note that ARSA activity in LI patients has continued to

decline, and is now, on average, at the lower limit of the reference range for healthy adults. This is in line with the ERG report, where we noted that continued decline in ARSA activity would bring level to, or below, this lower limit.

The company claims that "… it is normal, physiologically, for CSF enzyme levels to fluctuate between samples…"; however, there is no evidence of such fluctuation. Within-patient levels of ARSA show a consistent decline in most of those patients with declining levels. If ARSA levels were fluctuating within the normal range we would expect to see some patients with higher than average levels; there were none. The ERG therefore does not consider that fluctuating measurements is a valid explanation for the low levels of activity in many patients.

Figure 1 ARSA activity in CSF (from new data appendix)

Given the totality of the data on both GMFC-MLD and CSF-ARSA activity, the ERG is increasingly concerned that the assumption of a life-time benefit is inappropriate. While is difficult to accurately estimate an appropriate rate of progression given the limited data set, it is the ERG's view that 20 years average stability is a reasonable estimate given the observed rates of decline. This therefore forms the ERG's preferred assumption in the updated base-case. It should be noted that this does allow for very long periods of stability in some patients but also reflects more immediate drops in others, as appears to be the case in the most recent data cut.

6 SUBSIDIARY ISSUES

6.1 Cryopreserved formulation of OTL-200

The ERG notes that its primary concern here has always been the lack of evidence on the cryopreserved formulation, given that this is the form intended for use. The new information provided by the company does not provide additional evidence for OTL-2000, and so the ERG reiterates its original concern.

The ERG notes that no new data on the cryopreserved formulation trial are available. It is unclear why no new data analysis appears to have performed since 2019. The ERG assumes that longer follow-up on ARSA activity, and some early outcome data, should have been collected during 2020, and it is unfortunate that this is not available for assessment, given the critical importance of demonstrating effectiveness with the cryopreserved formulation.

6.2 Proportion of MLD variants

No further evidence is presented by the company regarding the distribution of patients across MLD subtypes. The company acknowledges the uncertainty regarding these parameters and is broad agreement regarding the approach adopted in the ERG base-case is reasonable and makes the best use of the limited available data. No further analysis is present by the ERG regarding the distribution of patients across subtypes.

6.3 Diagnosis of [redacted] and [redacted]

The ERG accepts the clarifications on the two patients with regard to symptoms at diagnosis. However, it remains unclear whether the disease course of patients [redacted] and [redacted] is representative of that typically seen in those diagnosed with early juvenile MLD. Patient [redacted] in particular appears to have experienced extremely slow progression of symptoms relative to the natural history cohort. There are clearly no patients in this group who experience such limited progression over such a long period of time.

While patients [redacted] and [redacted] may have been diagnosed as early juvenile, their disease course prior to treatment with OTL-200 may resemble later juvenile forms of the condition. They therefore continue to create a problem with regards to the comparability of the trial, NHx datasets, and the general population of ES-EJ patients. The influence of these patients upon the modelled progression modifiers may mean these multipliers do not adequately represent the relative progression of MLD.

6.4 Progression modifiers

The company's revised base case includes revisions to the progression modifier applied in the ES-EJ group. The progression modifier determines the speed at which unstable patients progress through the GMFC-MLD health states relative to standard care. The revisions made by the company act to decrease the rate of progression in GMFC-MLD 0, 1 and 2. The company justifies this revision on the grounds that the new data cut provides sufficient evidence to re-estimate this parameter.

As stated in the ERG report the, ERG cannot fully verify the methods used generate the progression modifier and considers that there is limited justification for the application of different progression

across the different MLD variants given the limited evidence available. The changes act to reduce the ICER by approximately £30,000 per QALY, see Section 7 for relevant scenario analysis.

7 ADDITIONAL ERG ANALYSIS

The results of additional scenario implemented by the ERG on the alternative company base case are presented in Table 4. This considers the following scenarios:

- Scenario 1 - Response rate used to classify patient's trajectory are revised in line with the decision rules previously proposed the ERG using the new data cut. See section 3.1 for modelled response rates.
- Scenario 2 - Progression modifiers used in the ES-EJ are equalised with those used in the other variants.
- Scenario 3 - Utilities are revised to align with ERG's original preferred utility set removing all decrements associated with cognitive impairment. These utilities are applied to all groups.
- Scenario 4 - Utilities are revised to align with full rescaled utility set proposed by the company. This scenario includes decrements associated with cognitive impairment but does not include the top up QALYs proposed by the company.
- Scenario 5 - Alternative stabilisation assumptions are explored.

In Table 5 the ERG presents a revised base-case this combines Scenarios 1, 2, 3 and 5b. Additional scenario analysis is also presented to consider uncertainties regarding the appropriate utility set and durability of stabilisation.

Table 3: Additional ERG scenarios using Company Alternative Base case

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
Alternative Company Base Case																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 1: ERG revised response rate																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 2: Progression modifiers equalised across all groups.																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 3: ERG preferred utilities excluding cognitive decrements																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 4: Company's rescaled utility set including utility decrements																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 5a: 10 year average stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															

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
Scenario 5b: 20 year average stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 5c: Lifetime stabilisation																
BSC	[redacted]															
OTL-200	[redacted]															

Table 4: ERG revised base-case and selected scenario analysis

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
Revised ERG base-case																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 1: Rescaled utility set including utility decrements																
BSC	[redacted]															
OTL-200	[redacted]															
Scenario 2a: 10 year average stabilisation																
BSC	[redacted]															

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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2b: Lifetime 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]

8 APPENDIX A

Table 5 Classification of response for individual patients

	Original company base-case	Revised company base-case	Original ERG base-case	Revised ERG base-case
Pre-symptomatic Late infantile				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-symptomatic early juvenile				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early symptomatic Early Juvenile				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* No new data available