NICE National Institute for Health and Care Excellence

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ID1666 OTL-200 for metachromatic leukodystrophy

Lead team presentation

1st HST committee meeting

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15th April 2021

Metachromatic leukodystrophy (MLD)

Metachromatic leukodystrophy (MLD) is a rare hereditary disease that involves the inability to breakdown lipids that contain sulphate (sulfatides). This leads to an accumulation of sulfatides that causes destruction of the protective fatty layer (myelin sheath) surrounding nerves

Prevalence

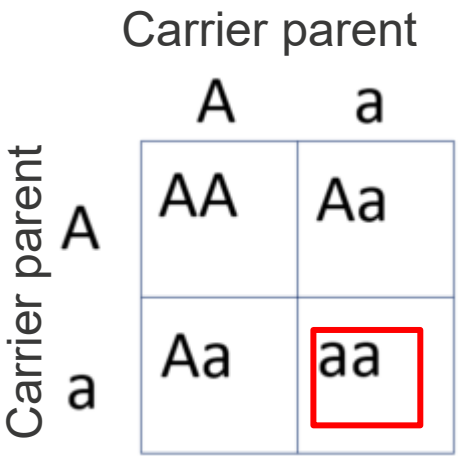
- Currently, 29 known MLD cases in UK (13 late infantile, 6 early juvenile and 10 adult) → prevalence of ~0.04 in 100,000
- Birth prevalence ~6.8 per million live births in UK → about 4–5 babies with MLD every year in England and Wales (based on 640,370 live births in 2019) → about XXX will be eligible for treatment with OTL-200

Disease course

- Clinical course can be broadly divided into pre-symptomatic stage with normal motor and cognitive development, followed by a developmental plateau and early onset of first symptoms (early symptomatic)
- Rapid and predictable trajectory of progression → neurodegenerative, developmental stagnation, loss of abilities in motor function, language and cognition resulting in a decerebrated state and premature death

Pathogenesis

- MLD is caused by mutations to the arylsulfatase A gene (ARSA) that encodes production of arylsulfatase A
- MLD is an autosomal recessive genetic disorder – in most cases both parents are carriers of a mutated ARSA gene and one functional ARSA gene (leading to a 25% chance of having an affected child)



- Association with specific mutations and the subtype of MLD (genotype-phenotype correlation), dependent on whether there is residual function of the mutated ARSA gene (residual allele/R) or no function (null allele/0)
- ARSA is essential for sulfatide metabolism – deficiency results in accumulation of sulfated glycolipids, particularly in the myelin sheaths of the nervous system, and to a lesser extent in visceral organs
- With progressive accumulation of sulfatides, the lysosomal-endosomal system becomes dysfunctional, and other secondary pathogenic cascades occur, ultimately resulting in cell death

Main clinical forms of MLD

	Phenotypic type	Age of symptom onset	Disease progression	Survival at year	
				5	10
Early onset	Late Infantile (LI) 40-60% of MLD	up to 30 months	2 null alleles (0/0 genotype), no residual ARSA activity Most aggressive form, highly predictable and severe disease leading to early death Usually presents with motor symptoms	25%	0%
	Early Juvenile (EJ)	between 30 months and 6 years	1 null allele and 1 residual allele (0/R genotype) or less frequently 2 residual alleles (R/R genotype) Slower, more protracted initial disease progression than LI. Can present with either cognitive or motor symptoms. Once patients cannot walk independently, disease progression occurs at same rate as LI	70%	44%
Late onset	Late Juvenile (LJ)	between 7 and 16 years	Cognitive and behavioural symptoms before motor function deteriorates. More prolonged, less rapid disease progression compared to LI and EJ	NR	NR
	Adult	from 17 years		NR	NR

Early onset only included in company decision problem (as per marketing authorisation)

Diagnosis and screening

MLD suspected if there is:

- Motor and/or behavioural/cognitive symptoms
- Family history (neurological disease / age of onset) and physical examination (gait abnormalities, spasticity, decreased muscle stretch reflexes)
- Magnetic resonance imaging (MRI) evidence of demyelination (but in early stages, normal MRI may not rule out MLD)

MLD confirmed by enzymatic panels and genetic analysis:

- ARSA activity: measured in isolated blood leukocytes and levels checked against normal controls
- Molecular genetic analysis of ARSA gene: low ARSA activity possible in individuals without MLD → confirm diagnosis (homozygosity or compound heterozygosity for ARSA-MLD variants)
- Urinary sulfatides: sulfatides accumulate in urine 10- to 100-fold higher than normal controls

MLD current treatment

Current treatments

No national guidelines on MLD. There are no standard disease-modifying treatment options available for early onset disease and patients are provided with best supportive care (BSC) to manage disease complications and maintain quality of life. This may include:

- physiotherapy (mobility and respiratory)
- management for pain and skeletal deformity
- dietary support
- drugs to reduce spasticity, seizures and psychiatric symptoms
- family and psychological counselling

Treatment centres

In England, MLD is managed by local paediatric specialists who refer people to a paediatric lysosomal storage disease (LSD) specialist centre for multidisciplinary treatment led by a paediatric metabolic consultant. England has 3 LSD specialist paediatric centres:

- Great Ormond Street Hospital London
- Birmingham Children's Hospital
- St Mary's Hospital Manchester

Patient and carer perspectives

Patient expert submissions

2 submissions from parent/carer patient experts

Living with MLD

- Route to diagnosis is not straightforward – early motor problems can be misdiagnosed as muscle weakness/dyspraxia, and episodes of sensory processing issues misdiagnosed as behavioural problems
- At later stages of the disease, untreated children with MLD:
  - are unable to walk, with painful spasticity, musculoskeletal deformities
  - are unable to see, hear and communicate their needs
  - have complex gastrointestinal issues and are doubly incontinent
  - have epilepsy, dementia and reactions to sensory stimuli
  - are dependent on full-time carers
- The burden on parents, carers and families is substantial:
  - Carers forced to leave employment to provide care
  - Mental health issues including depression, loss of income and freedom, breakdown of relationships, grief and sleep deprivation
  - Affects siblings and family, pressure of adopting a carer's role and avoidance of social situations

Patient expert submissions

Current treatment

- Lack of support from local paediatricians and some metabolic consultants – lack of experience in dealing with MLD
- Many families experience frustration with the speed of NHS services, particularly in relation to the supply of specialist equipment (e.g. bespoke wheelchairs, sleep systems and positioning aids). By the time items are procured, assessments are out of date and recommendations are redundant
- Physiotherapy is of particular importance with regard to alleviating and preventing serious muscle and bone complications

The technology

- Remarkable outcomes – children that are treated at a younger age show no signs of the disease many years after transplant
- Some children are able to attend full-time mainstream schools
- Straightforward one-off procedure (4 months in Italy for treatment is burdensome for families) – some side effects related to chemotherapy (including sickness, mucositis, hair loss and incontinence) but well tolerated after initial treatment
- No further progression after 18 months, some further physiotherapy required

Patient organisation submissions: Patients

Patient and caregiver burden survey

- 3 organisations (ArchAngel MLD Trust; The MPS Society; MLD Support Association UK) conducted a survey of 20 families, representing 24 children (over 50% of all UK patients)

Patient	Mobility	60% LI and 100% EJ children require wheelchair at diagnosis – all children currently require a wheelchair
	Communication	80% LI (mean age 5.7 years) and 100% EJ children had lost their ability to speak
	Ability to swallow	All patients were fed by gastrostomy or nasogastric tube
	Continence	All patients progress to double incontinence by the end of life stage Constipation and urinary retention are also common
	Eyesight and hearing	100% EJ children are blind – not routinely assessed
	Respiratory issues	80% LI and 100% EJ children experience aspiration, excess secretions and chest infections that require regular suctioning
	Pain/musculoskeletal	80% LI and 100% EJ children reported both dystonia and hypertonia – unclear sources of pain because of communication
	Neurological issues	80% LI and 67% EJ surveyed children receive anti-seizure medication
	Support	LI children needed 1:1 or 2:1 support starting at an average age of 2.4 years; EJ children required support at an average of 6.3 years

Patient organisation submissions: Carers

Carer	Care burden	Constant support needed from parents/carers, professional support from professional carers, hospices and respite care
	Mental health	Common feelings are intense grief, extreme stress, depression, anxiety, panic, isolation, anger, guilt
	Financial impact	75% LI and 67% EJ families had 1 parent leave employment 25% LI and 33% EJ families, both parents stopped working Substantial additional costs incurred outside of direct hospital care
	Relationships	Report 'severe marital problems', wide-ranging impact on siblings, friendships and relationships with wider family and friends are affected

Patient organisation activities

- Providing support and information to families of patients with MLD
- Providing funding of specialist equipment (e.g. bespoke seating and positioning/sleeping aids), home adaptations, physical therapies and respite care
- Campaigning to have all UK babies screened for MLD (and other rare diseases) at birth

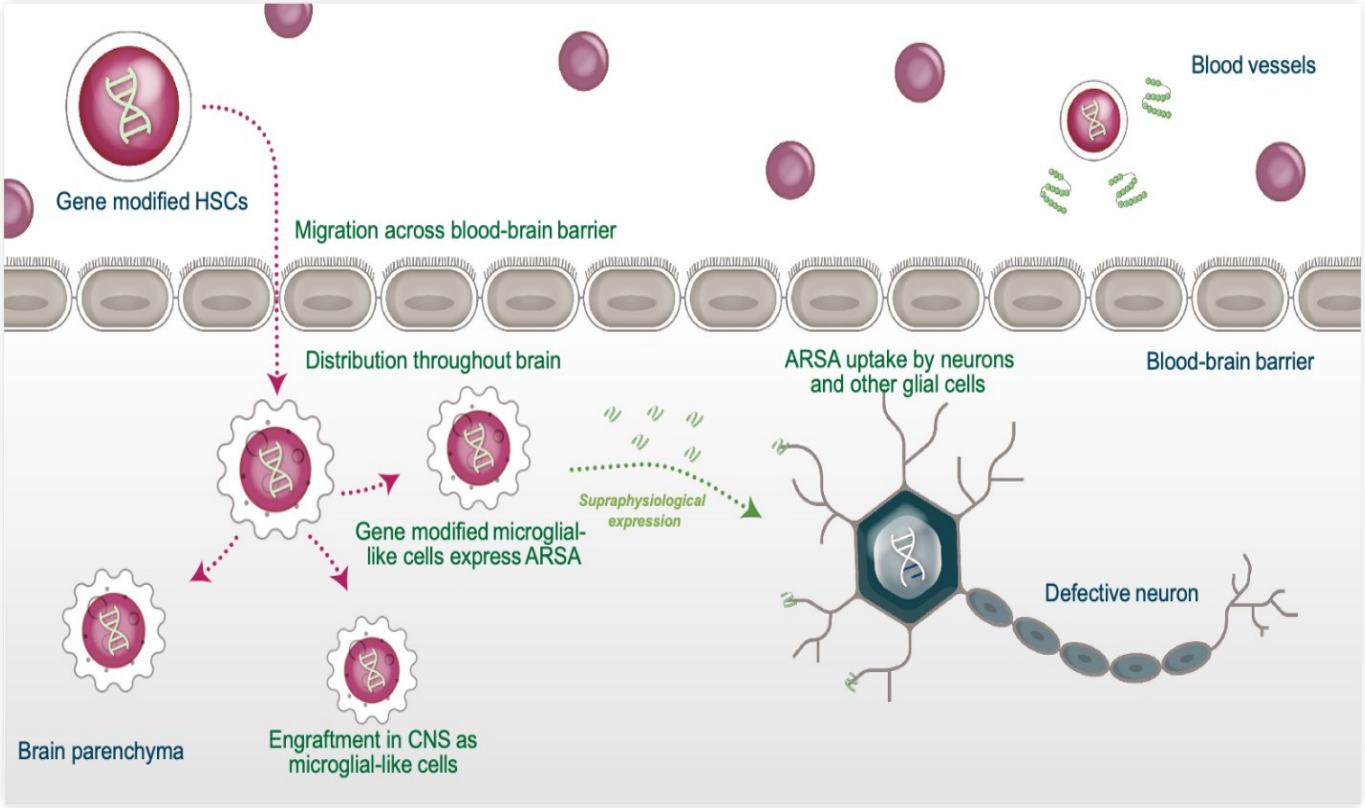
Decision problem

OTL-200, autologous CD34+ cells encoding ARSA gene (Libmeldy, Orchard Therapeutics)

Marketing authorisation	Marketing authorisation obtained on 15th October 2020. Orphan drug designation (13th April 2007) "… for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arysulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity: • in children with **late infantile or early juvenile forms, without clinical manifestations** of the disease • in children with the **early juvenile form, with early clinical manifestations** of the disease, who still have the ability to walk independently and before the onset of cognitive decline."
Administration and dose	• **Cryopreserved** dispersion of patient's own stem cells administered only once by intravenous infusion via central venous catheter at a qualified treatment centre with experience in haematopoietic stem cell transplantation • Myeloablative conditioning with busulfan (recommended) is needed before infusion to promote efficient engraftment of cells. Use of myeloablative or sub-myeloablative regimen and use of patient bone marrow harvest or mobilised peripheral blood are at physician's discretion

Mechanism of action of OTL-200

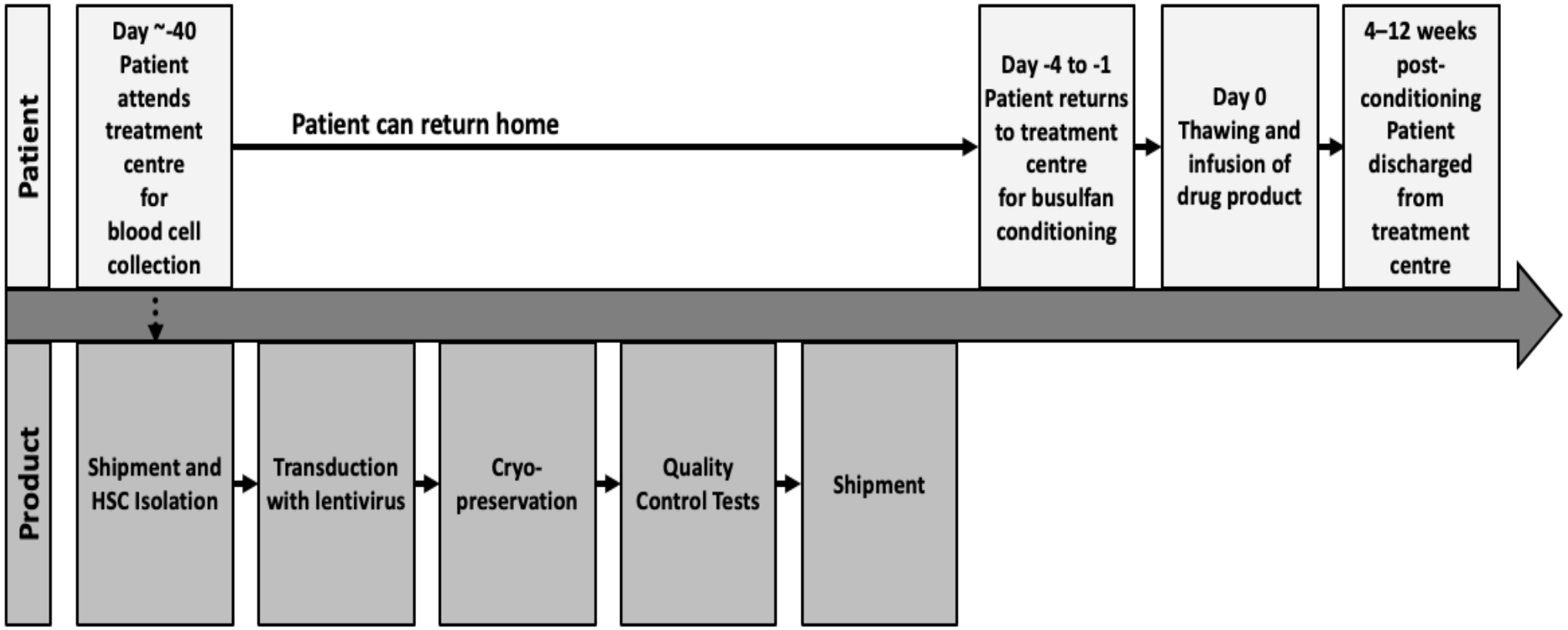
- Ex vivo genetically modified autologous CD34+ haematopoietic stem and progenitor cells (HSPC) gene therapy
- HSPCs are collected from patient bone marrow or peripheral blood, and transduced with a lentiviral vector, which inserts copies of human ARSA complementary DNA into cell genome
- Genetically-modified cells secrete functional ARSA enzyme, that are absorbed by surrounding cells (cross-correction), and used to break down or prevent build-up of harmful sulfatides



Company: on successful engraftment, OTL-200 works to repopulate brain with self-renewing gene corrected stem cells that make ARSA enzyme:

- preventing onset of MLD in pre-symptomatic 'full responders' or
- stopping or slowing MLD progression in pre- and early-symptomatic 'partial responders'

OTL-200 administration



- Patient eligibility confirmed → treatment starts with cellular source harvest
- After blood cells are collected, patient returns home → OTL-200 is manufactured → product **cryopreserved** until patient is ready to have treatment
- Patient stays for 4 to 12 weeks after myeloablative conditioning. Standard procedures for management after HSPC transplantation
  - Range of XXXX days seen in trials likely to be similar in real world commercial setting; median of XX days likely to be reduced as more clinical experience is gained

Decision problem: Population

NICE scope	Company submission	ERG comments

People with MLD	**Narrower to reflect marketing authorisation**
	• Biallelic mutations in ARSA gene:
	  ○ in children with LI or EJ, no clinical manifestations of MLD **(pre-symptomatic LI / EJ)**
	  ○ in children with EJ, with early clinical manifestations of MLD, who can walk independently (GMFC-MLD score ≤ 1) and before onset of cognitive decline (IQ ≥ 85) **(early-symptomatic EJ)**
	• **Recommended that treating physicians should check at both cell harvest and conditioning stage that patient is not in rapidly progressive phase of MLD**
		Discrepancy between upper age limit for onset for EJ in OTL-200 trial (<7 years) and classification system (<6 years)
		• ERG's clinical adviser: age category terms are used relatively loosely, 1 year difference in definitions unlikely to be important in clinical practice
		• NB: only 1 patient in OTL-200 trial had an age of onset between 6 and 7 years
		Definition of "early symptomatic" is unclear
		In **EPAR**, early symptomatic was defined in different ways:
		• within 6 months after first reported symptom
		• subjects with an **IQ ≥70 and ability to walk independently for ≥10 steps**
		• **IQ ≥85 and GMFC-MLD ≤1** (i.e. patient has ability to walk independently and before onset of cognitive decline)

⊙ ***How would patients in the NHS be identified and assessed for eligibility of OTL-200, in particular with respect to age threshold and 'early symptomatic' status?***

⊙ ***For patients eligible for OTL-200, how likely is it that they could become ineligible between harvest and transplantation?***

Decision problem: Intervention

NICE scope	Company submission	ERG comments
OTL-200	OTL-200 **fresh formulation** and **cryopreserved formulation (will be used commercially)**	• Most of efficacy and safety data relate to **fresh** product • Data used in economic model are from **fresh** formulation

Decision problem: Comparators

NICE scope	Company submission	ERG comments

Established clinical management without OTL-200, including but not limited to:
• Stem cell transplant
• Best supportive care (BSC)
	• BSC reflects current UK clinical practice
	• Allogeneic haematopoietic stem cell transplantation (HSCT) not included as it is mainly used in late-onset MLD (view shared by 6 UK MLD experts)
		• **BSC** includes management of dystonia, infections, seizures or secretions; pain relief/sedative drugs; feeding support (including gastrostomy); psychological and social support (including specialist schooling); genetic advice and planning; and end of life care
		
		• **HSCT**
		  ○ Disagrees with total exclusion
		  ○ ERG's clinical advisor: HSCT used and there may be overlap between patients eligible for HSCT and OTL-200
		  ○ Evidence on HSCT is limited, but suggests that in appropriate patients, it is effective at delaying MLD progression and prolonging survival. If included, may reduce comparative effectiveness of OTL-200

⊙ ***Is HSCT a relevant comparator for OTL-200 indicated population?***

Decision problem: Outcomes (1)

NICE scope	Company submission	Assessment
Change in gross motor function	Gross motor function	• Gross Motor Function Measure (GMFM) [**co-primary endpoint** of registrational study: 10% improvement in GMFM score vs historical control] • **Gross Motor Function Classification in MLD (GMFC-MLD)** – used in **economic model**
Change in ARSA activity	Reconstitution of ARSA activity	Measurement of ARSA activity in: • Haematopoietic system performed on peripheral blood mononuclear cells (PBMCs), bone marrow (BM) mononuclear cells, and other peripheral blood and BM subpopulations • **Cerebrospinal fluid (CSF)** (indirect evidence that transduced cells have migrated to CNS and are **producing and secreting functional ARSA enzyme**) [**co-primary endpoint** in registrational study: statistically significant (≥2 SD) increase in residual ARSA activity vs pre-treatment values measured in PBMCs at Year 2 after treatment]
Change in neurocognitive function	Developmental quotient (DQ)	• Cognitive abilities assessed using neuropsychological tests against norm: age equivalent and DQ NB: In past, IQ scores used; issue with floor effect for IQ <40 - used in **economic model**

Decision problem: Outcomes (2)

NICE scope	Company submission	Assessment
Change in neurological function	Brain MRI	• Brain MRI measured demyelination and atrophy with adapted Loes' scoring system (0 = normal to 31.5 = markedly abnormal; score >0 is considered abnormal) NB: Possible quantitative biomarker of disease severity
Stability of nerve conduction	Nerve conduction velocity (NCV)	• NCV from electroneurography recordings assessed peripheral neuropathy NB: Peripheral neuropathy often precedes CNS manifestations of MLD, especially in LI, and contributes to gross motor impairment
Mortality Age and time at severe motor impairment or death	Survival outcomes	• Overall survival: potential confounding by different approaches of families and health systems in receiving supportive care in advanced stages of MLD • Composite time to severe motor impairment or death (sMFS): interval between birth and loss of locomotion and loss of sitting without support (GMFC-MLD ≥5) or death
Health related quality of life	Not assessed in OTL-200 studies	

⊙ ***What are the most important outcomes for patients?***

Clinical evidence

OTL-200 clinical studies in submission

Objectives	Study number (Status)	Study design	Patient population	Duration of follow up
Evaluate safety and efficacy of **fresh** formulation of OTL-200	Phase I/II trial Study 201222 TIGET-MLD (follow up only; NCT01560182) – **registrational trial**	Non-randomised, open-label, prospective, comparative (non-concurrent control), single-centre study	20 PS-LI, PS-EJ or ES-EJ	At least 8 years post treatment
	EAP CUP207394 (follow up only)	Compassionate use programme	1 ES-EJ	Initially treated in 2013
	EAP HE205029 (follow up only)	Hospital exemption	3 PS-LI	Initially treated in 2016
	EAP CUP206258 (follow up only)	Compassionate use programme	4 PS-LI, 1 PS-EJ	Initially treated in 2016
Evaluate efficacy and safety of **cryopreserved** formulation of OTL-200	Phase II trial Study 205756 (follow-up only; NCT03392987)	Open trial	10 PS or ES early onset MLD patients (LI, EJ or intermediate between LI/EJ) **enrolled** • n=6 reported in submission	Until 8-year follow-up visit

Ongoing trial enrolment/data collection

Objectives	Study number (Status)	Study design	Patient population	Duration of follow up
Evaluate efficacy and safety of **cryopreserved** formulation of OTL-200	Phase III trial (**enrolling** started June 2020; NCT04283227)	Open label, non-randomized trial	Up to 6 **late juvenile (LJ)** • If symptomatic: MLD onset ≥7 and <17 years • If pre-symptomatic: MLD onset <17 years at treatment, and a sibling diagnosed as LJ (disease onset ≥7 and <17 years with biochemical and molecular diagnosis) • **Outside of indicated population**	Planned follow-up 12 years (until January 2032)
Characterise long-term efficacy and safety of OTL-200	Long-term follow up study - in discussion with EMA as part of marketing authorisation (risk management plan)		XXXX patients previously treated with OTL-200 in clinical development and post-authorisation	15 years post-treatment follow up

⊙ ***What is the current status of the ongoing data collection and long-term study?***

Clinical evidence for OTL-200

- 2 clinical studies (registrational study, 201222 using fresh formulation and study 205756 using commercial cryopreserved formulation)
- 3 expanded access programmes using fresh formulation (enrolment criteria, study design and efficacy endpoints similar to Study 201222)

In total XXXXXX patients in integrated data set were analysed for the indicated population (**fresh formulation only)**:

- XXX patients with PS-LI
- XXX patients with PS-EJ
- XXX patients with ES-EJ

Study 201222 selection criteria

Inclusion criteria	• Biochemical and molecular diagnosis of MLD: ARSA activity below normal range and 2 disease-causing ARSA alleles (known/novel mutations). Novel mutation(s): 24-hour urine collection shows elevated sulfatide levels
	Eligible patients must have either:
	• An older sibling affected by MLD (index case), whose age of symptom onset was ≤ 6 years (not celebrated 7th birthday)
	• If no older sibling, investigator-assessed patient has early onset MLD likely to benefit from gene therapy, and is ≤ 6 years (not yet 7 years)
	• Classified by symptom onset and genotype:
	  • LI (onset ≤30 months and genotype 0/0)
	  • EJ (onset 30 months to 6 years and genotype 0/R)

Included in trial but excluded from efficacy analysis	**4 patients excluded from company efficacy analysis. Rationale:** • Indicated patients GMFC-MLD ≤ 1 and IQ ≥ 85 • SmPC: "physicians should ensure no deterioration has occurred between screening and commencement of cellular harvest" to exclude rapidly progressive phase of disease

ERG comments

- 1 ES-EJ patient met eligibility criteria but excluded due to "rapid progression": [redacted]
- Company has not provided data to justify "rapid progression" → patient should be included in the analysis

Other expanded access programmes

- **Compassionate Use Programmes**
  - **CUP 207394**: 1 ES-EJ patient
    - Enrolment in Study 201222 closed and did not meet inclusion criterion of ≤ 6 months from onset of symptoms (symptomatic for 8 months)
      - Protocol subsequently amended to IQ ≥70 and can walk ≥10 steps (met all other eligibility criteria)
    - Conducted at same clinical site and by same study site staff and followed Study 201222 design where appropriate
  - **CUP 206258**: 5 PS patients
    - Enrolment criteria, study design and efficacy endpoints similar to Study 201222 but maximum dose increased from 20×10^6 cells/kg to 30×10^6 cells/kg

- **Hospital Exemption Programme, HE 205029**: 3 PS patients
  - Enrolment in Study 201222 closed, no other OTL-200 clinical trials recruiting
  - Enrolment criteria, study design and efficacy endpoints were similar to those defined for Study 201222

Company natural history cohort approach

Comparator arms from historical controls: OSR-TIGET natural history (NHx) cohort study

- n=31; 19 LI, 12 EJ
- Enrolling since 2004; prospective and retrospective data used
- Patients received best supportive care aimed at managing disease complications and maintaining quality of life

- **NHx cohort** consisted of all eligible patients that could reliably be included (no individual patient matching)
  - Patients selected for matched analysis were LI and EJ patients who had a study visit at which their chronological age fitted within the range of ages for patients treated with OTL-200
- **Matched sibling analysis** undertaken but number of suitable patients was very small (n=12 treated with OTL-200 and n=11 corresponding untreated siblings from NHx cohort)

ERG general comments on OTL-200 evidence

- OTL-200 only fully tested on 35 patients, very small numbers for each subgroup (LI, PS-EJ or ES-EJ)
- Company submitted limited patient baseline and results data, especially for NHx cohort and did not report details of statistical analyses performed
  - ERG unable to properly critique methods of analysis and unable to compare important baseline characteristics across OTL-200 and comparator cohorts
  - Interpretation of submitted comparative analyses including possible impact on results of clinically relevant differences in factors such as age at disease onset (or predicted age) and genotype between OTL-200 and NHx cohort was difficult
- Untreated sibling comparator analyses should be most robust in terms of reducing concerns about bias (expected to have same genotype and very similar age at disease onset) but are limited by sample size and number of data points available for untreated siblings

Gross motor function outcome measures

Company used 2 assessment tools to measure gross motor function:

- **GMFM**: 2 versions (GMFM-88 and GMFM-66), age-related 4-point scale assessing 5 dimensions (lying and rolling; sitting; crawling and kneeling; standing; walking, running and jumping) in children 5 months to 16 years. Total score from 0% to 100%. A 5-year old child without motor disabilities is able to reach maximum score of 100% – **trial co-primary endpoint**
- **GMFC-MLD**: based on ability to walk; assesses children only from 18 months onwards. Score from GMFC 0 (normal) to GMFC 6 (loss of all gross motor function) – used in **economic modelling**

GMFC-MLD level	Description
0	Walking without support with quality of performance normal for age
1	Walking without support but with reduced quality of performance, that is, 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

⊙ ***What are the expected differences between GMFM and GMFC-MLD?***
⊙ ***Are the GMFC-MLD levels representative of patient experience?***

Study 201222: GMFM in PS-LI

NB: OTL-200 previously called GSK2696274 / GT (blue lines)

NB: not shown 3 patients from HE study and 4 patients from CUP studies

Increasing GMFM values better

Patient excluded from indicated population because treatment initiated just after disease onset during rapidly progressive phase of disease

Study 201222: GMFM in EJ (PS and ES)

NB: OTL-200 previously called GSK2696274 / GT (blue lines)

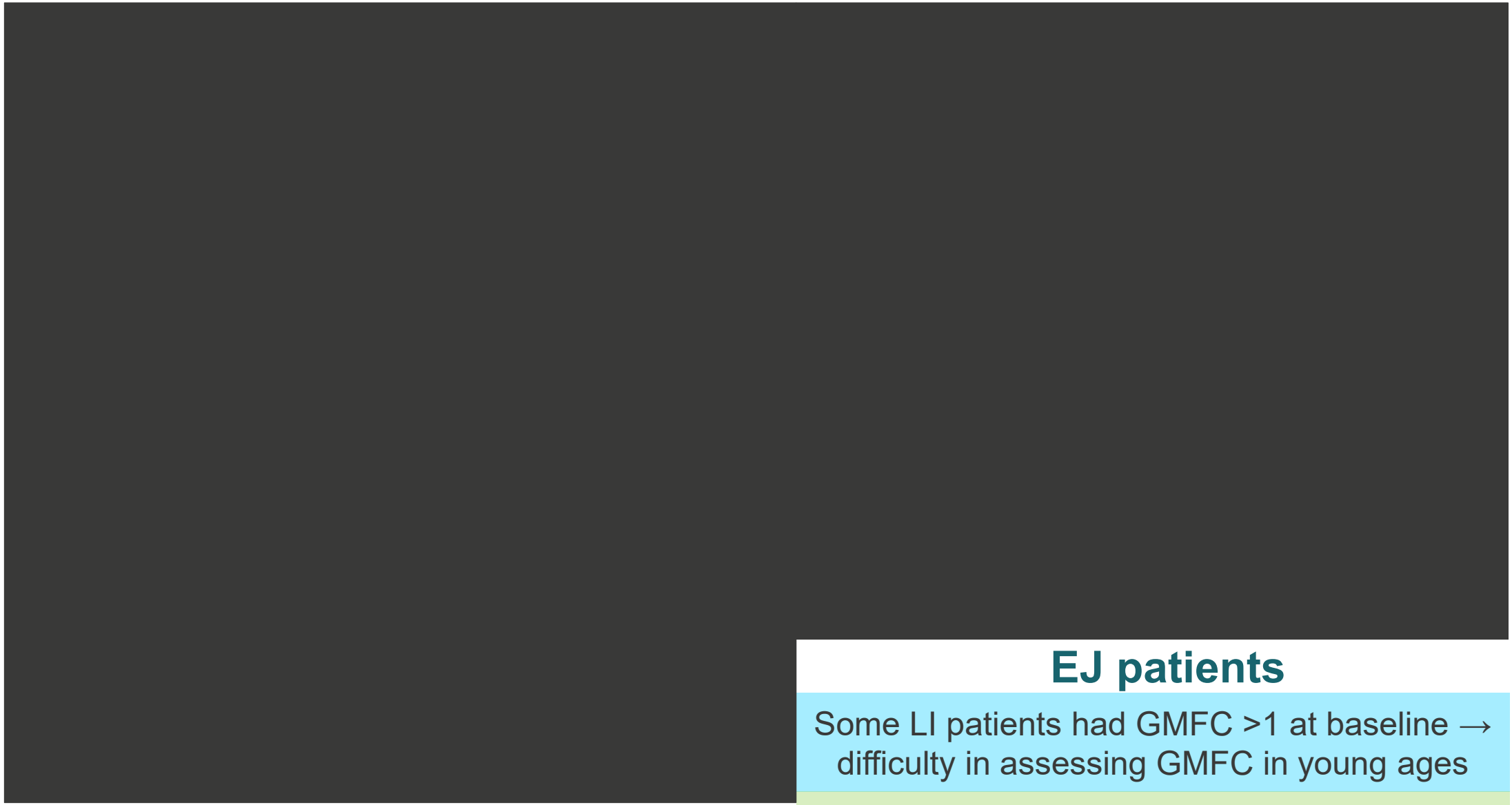
NB: not shown 2 patients from CUP studies

Increasing GMFM values better

ERG disagrees with company exclusion of 1 ES-EJ patient

Patients excluded from indicated population because treatment initiated just after disease onset during rapidly progressive phase of disease

GMFC panel plots in PS-LI and EJ (PS and ES)



PS-LI patients

EJ patients

Some LI patients had GMFC >1 at baseline → difficulty in assessing GMFC in young ages

Some patients show decline at last follow up → unclear if this represents gradual decline or stabilisation

ARSA activity in peripheral blood mononuclear cells (PBMCs)

[redacted]

ERG comments

- ARSA activity [redacted], but insufficient data to determine if this is a meaningful difference

ARSA activity in cerebrospinal fluid (CSF)

ERG comments

- Company: [redacted]
- Company: Activity in CSF not measured 60 to 90 months → no further data currently available
- [redacted] → [redacted]

- ***What is the difference between ARSA activity in PBMCs vs CSF?***
- ***What is the clinical significance of the changes observed in ARSA activity?***

ERG comments on developmental quotient (DQ)

LI: scores consistently [redacted]

NHx: declined to almost 0 by age 4. Fluctuations within each patient profile makes it difficult to assess if patients are improving, declining or remaining stable over time

PS-EJ: response pattern seems broadly similar to LI but limited data. [redacted] patients may have declining scores over time, after initial increases, but do not fall into cognitive impairment levels during follow up

ES-EJ: [redacted]. Scores of most patients are consistently high, but substantial fluctuations make assessment of trends difficult

- ***What is the clinical significance of the changes observed in DQ?***
- ***Is there a relationship between cognitive and gross motor function decline?***

ERG comments on brain MRI total scores

LI: scores consistently low (0 is normal, >0 is abnormal), and lower than all results in NHx group
Reasonable evidence OTL-200 materially improves scores

PS-EJ: scores generally below those in NHx group, but with limited data
Plausible evidence that OTL-200 materially improves scores

ES-EJ: scores are below average for NHx group, but several are within range seen in NHx patients, especially if [redacted] is excluded
No convincing evidence that OTL-200 improves scores

ERG graph: brain MRI total scores for PS-LI and PS-EJ

ERG comments

- [redacted]
- [redacted]
- [redacted]

⊙ ***What is the clinical significance of the changes observed in brain MRI scores?***

ERG comments on nerve conduction velocity (NCV) Index

PS-LI: most patients had higher NCV scores than for NHx group → OTL-200 may reduce progressive peripheral neuropathy in some patients
Scores are still well below the expected score for healthy children (a score of around 0)

EJ: interpreting results is complicated by very limited data
OTL-200 does not appear to improve peripheral neuropathy. On average, NCV scores are worse for patients having OTL-200 than for patients in NHx group, but are within range of values in NHx group

ERG graph: Nerve Conduction Velocity (NCV) in PS-LI and PS-EJ

ERG comments

- [redacted]
- [redacted]
- [redacted]

- ⊙ *What is the clinical significance of the changes observed in NCV scores?*
- ⊙ *Is there a relationship between NCV changes and gross motor function decline?*
- ⊙ *Based on the mechanism of action, is OTL-200 expected to affect the central and peripheral nervous system equally?*

Kaplan-Meier curve for overall survival (PS-LI vs NHx)

Kaplan-Meier curve for overall survival (PS-EJ and ES-EJ vs NHx)

Company clinical evidence interpretation: full/partial response and stabilisation

Company proposes (and includes in economic model) 3 categories of response:

- **Full responders:** patients treated before symptom onset, and remain symptomatically stable with motor and cognitive function fully intact (assumption: remain in GMFC 0 for full time horizon and lead normal healthy lives in line with general population)
- **Stable partial responders:** 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 stabilise in GMFC 1 or 2
- **Unstable partial responders:** patients in whom OTL-200 has failed to stabilise progression of symptoms. Patients progress through GMFC health states similar to BSC but at a slower rate

	Full responder N (%)	Stable partial responder (functional stabiliser) N (%)	Unstable partial responder (slowed progression) N (%)
PS LI (n = XX)	XXX	XXX	XXX
PS EJ (n = X)	XXX	XXX	XXX
ES EJ (n = X)	XXX	XXX	XXX

ERG comments on full response/partial response and stabilisation

- **Conceptual and biological rationale for full and partial response** but:
  - concerns that GMFC scores fail to capture subtle manifestations of MLD e.g. MRI scores and NCV scores show some evidence of disease progression in 'full responders'
- Concerns about validity of:
  - distinction between stable and unstable partial responders
  - assumption that all PS stable responders will stabilise at GMFC 1 or 2. Uncertain whether all patients with GMFC up to 2 will stabilise or continue to decline and stabilise at higher GMFC scores. Company's advisory board considered around XXX of partial responders would stabilise at GMFC 3 or 4 (**late stabilisation**)
- Accepts **biological rationale for late stabilisation:** aligns with evidence of established ARSA activity
  - Concerns that **many** partial responders **do not exhibit late stabilisation pattern** of disease progression (stable for at least 2 years, followed by decline). Small sample size and limited follow up → unclear if observed decline in GMFC function shows delayed treatment effect or continuous progression
- Company definition of full response did not require a minimum period of follow up
  - some patients classified as full responders with only very short follow up. **Establishing minimum follow-up period is difficult** given limited data but ERG suggests 12 months

ERG comments on durability of OTL-200 response/permanent stabilisation

- Company assumes full response is curative with permanent stabilisation
- Cannot make assumption only based on biological plausibility
  - EPAR: unforeseen and poorly understood issues such as **gene silencing** and unequal attrition of **high vector copy number (VCN) cell lines** (up to XXX) could lead to uncertainties with regard to sustained long-term efficacy.
  - Some OTL-200 patients who appeared stable over several years later experienced symptom decline. Decline in ARSA activity in CSF in LI after 24 months may be of concern as OTL-200 is intended to increase and maintain ARSA activity, EMA considers it likely that continued efficacy was dependent on **maintaining ARSA activity levels above a certain threshold**
  - Company suggests XXxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxX EMA could not verify this, evidence to confirm such a relationship was not provided
  - Evidence suggests that OTL-200 does not prevent disease progression across all systems equally → continued deterioration of peripheral neuropathy in EJ (PS and ES) was observed (NCV results). This may lead to motor function decline even in full responders

- ***Is the effect of OTL-200 likely to be permanent? How will this be defined?***
- ***In clinical practice, is it clear what defines a stabilised partial responder? How long does the patient have to be stable for to be defined as stable?***

ERG comments on adverse events

	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)

- Company did **not provide AE data for NHx cohort** → cannot confirm if none of SAEs were treatment-related but were instead related to myeloablative conditioning. Could not assess differences between subgroups
- **Myeloablative conditioning**: significant long-term **mortality risk** and AEs (e.g. dental problems, short stature, cognitive deficits, pulmonary dysfunction). **ERG scenario** using standardised mortality ratio of 1.25 to account for these risks
- Anti-ARSA antibodies reported in 4 patients, all events resolved spontaneously or after treatment with rituximab (also has possible AEs). **Anti-ARSA monitoring is recommended for up to 15 years after treatment**
- 3 deaths: 2 in patients with rapid disease progression; other unrelated to OTL-200 or MLD
- 19 patients had AEs related to **renal tubular acidosis or metabolic acidosis**, mostly in pre-treatment phase; 16 patients had **hepatobiliary** events during follow up

⊙ ***Are the side effects from conditioning clinically important?***

Cryopreserved formulation results

- 6 patients ([redacted]) from Study 205756: mean follow up [redacted]; 2 patients had baseline or 30 day data

ERG comments

- Immaturity of data and age of patients (GMFM is inconclusive at young ages) → surrogate ARSA activity in CSF is most reliable data
- ARSA levels in CSF [redacted]
- EPAR graphs: ARSA levels peak at around 1 year after treatment in patients having fresh formulation. EMA: ARSA CSF levels above 0.71nmol/mg/hr may be needed to achieve treatment effect in terms of GMFM stability (at least in PS-LI)

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]

⊙ *How is the cryopreserved formulation different from the fresh product?*

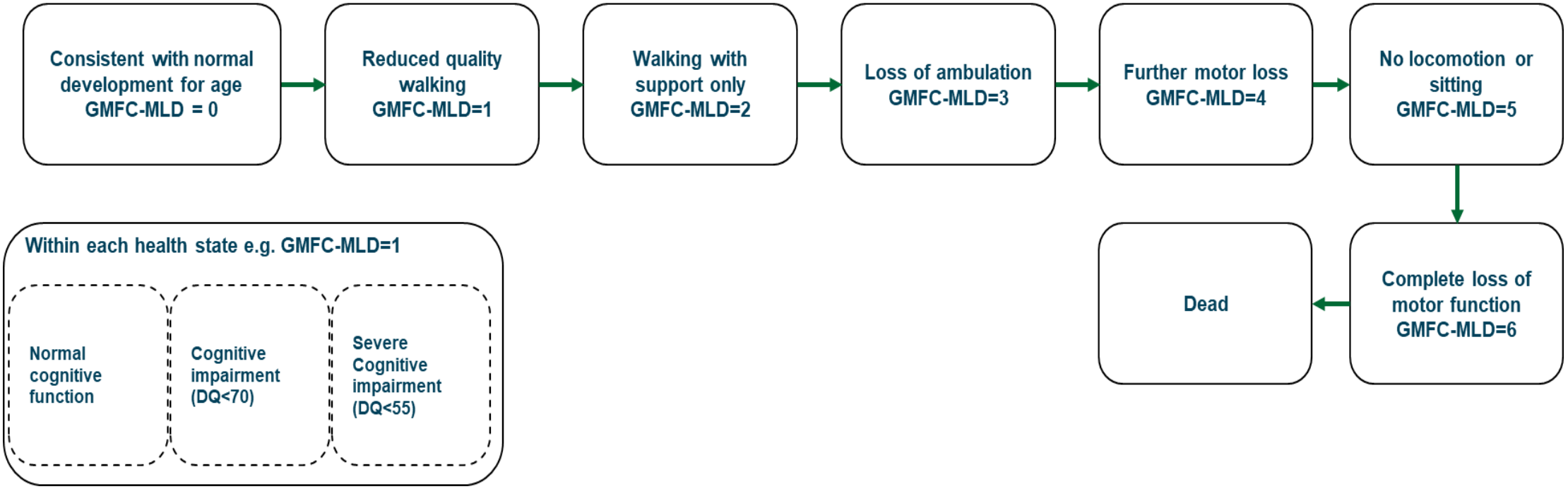
Key issues: clinical effectiveness

- What is the earliest age at which OTL-200 can be used? How soon after administration can a beneficial effect be seen?
  - What are the long term consequences of myeloablation including effects on mortality?
  - What minimum follow-up period is needed to determine if patients are stabilised at a specific GMFC level? Do patients stabilise above GMFC 2? Is the disease stabilisation permanent?
- Does OTL-200 have a differential effect on systems within the body?
  - How does a decline in cognitive function relate to a decline in motor function over time?
  - Does GMFC capture all important consequences of MLD that may respond differently to OTL-200 e.g. peripheral neuropathy, renal tubular acidosis, metabolic acidosis, hepatobiliary disorders?
  - What is the strength of relationship of ARSA levels with clinical outcomes?
  - Does decline in any of these outcomes affect mortality?
  - Are there any other important outcomes not considered?
- Is the evidence for the fresh formulation of OTL-200 generalisable to the cryopreserved formulation?
- Is HSCT a relevant comparator for OTL-200?
- What will be the effect of a newborn screening programme on the number of eligible patients?

Cost-effectiveness evidence

Economic model

Company model structure: Overview



- **Model type:** Markov model approximating partition survival model with 8 health states
- **Health states:** GMFC health states. For EJ only: treatment-dependent cognitive impairment (DQ) sub-states. Transitions only allowed to higher GMFC states
- **Population:** As per marketing authorisation (LI or EJ, GMFC 0 to 1, without severe cognitive impairment IQ ≥85): PS-LI, PS-EJ, ES-EJ modelled separately to allow for differences in baseline characteristics, natural history and efficacy of OTL-200 (separate and pooled ICERs)
- **Model overview**: Monthly cycle length, lifetime horizon (100 years), costs (NHS and PSS perspective), QALYs (patient and carers), 1.5% discount rate

Company model structure: GMFC inputs

Best supportive care

- Transitions between GMFC states: OSR-TIGET NHx cohort (matched for age and variant), published literature and expert clinical opinion
- Transition from GMFC 0 to 1 not reported in OSR-TIGET:
  - **LI:** published literature (Elgun 2019) on LI with start of follow up at 10 months
  - **EJ:** Clinical opinion suggesting average age of symptom onset was 30 months to 7 years
- Alternative rates of MLD progression for GMFC 2 to 5: Elgun 2019 and Kehrer 2011

OTL-200

- Assumed expected trajectory and transitions between GMFC states based on response and stabilisation status interpreted from clinical evidence:
  - **Full responders**: assumed patients are in GMFC 0 for lifetime and lead normal healthy lives in line with general population
  - **Stable partial responders:** assumed to permanently stabilise in GMFC 1 or 2 after initial progression (based on trial data and clinical expert opinion)
  - **Unstable partial responders:** assumed to progress through GMFC states at a slower rate than BSC – calculated compared to NHx cohort and expert elicitation

ERG comments on model structure

Model structure

- Lifetime horizon reasonable given curative potential of OTL-200
- BUT input parameters relevant to children are extrapolated to adults
  → short-term effectiveness evidence is projected over a very long period
  → increasing uncertainty in results

Model GMFC transitions

- Concept of stabilisation is difficult to validate because model structure is based on categorising and extrapolating unique response patterns observed in very few patients
- Clinical opinion and trial data are highly uncertain because of small numbers and limited follow up

Modelled population

Baseline characteristics

- Age based on data from OTL-200 trial and assumption:
  - **PS-LI (assumption):** earliest age (18 months) at which GMFC can be used
  - **EJ (OTL-200 trial data):** starting age at treatment
- Sex: based on demographic data on general population
- Level of cognitive impairment and starting GMFC: based on clinical opinion/assumption

ICER for pooled population

- ICERs for each group aggregated as a weighted average: based on expected incidence of patients across 3 groups informed by a structured expert elicitation process and evidence from epidemiological sources

Baseline patient characteristics

	Starting age (months)	Proportion male	Proportion with moderate cognitive impairment	Starting GMFC
PS-LI	18	49.3%	NA	All in GMFC 0
PS-EJ	45	49.3%	• 20% for BSC • 0% for OTL-200	All in GMFC 0
ES-EJ	80	49.3%	• 20% for BSC • 0% for OTL-200	• 40% in GMFC 0 • 60% in GMFC 1

ERG comments on modelled population

Concerns about baseline values and consistency with OTL-200 trial data

- Starting ages of PS-EJ (42 months) and ES-EJ (88 months) do not match data in Appendix A of company clarification response → little impact on results
- Starting age of 80 months in **ES-EJ** is significant mismatch with OSR-TIGET NHx cohort given starting GMFC 0 or 1.
  - In OSR-TIGET, EJ patients reach GMFC 4 at average age of 77 months and GMFC 5 at average age of 88 months

    → Company's assumption that more BSC patients would start with moderate cognitive impairment is unjustifiable

    → Baseline characteristics cannot differ by arm → introduces bias

    → **ERG corrected in 'Company corrected base case'**

- Modelled distribution of initial GMFC scores in **PS-LI** inconsistent with scores in Integrated efficacy analysis

  → may be due to difficulty of assessing GMFC in very young children

  → ERG considers assumed values reasonable

ERG comments on proportion of variants

ERG

- Do not reflect known MLD epidemiology (40-60% LI and 20-35% early/late juvenile)
- Results of elicitation process suggest large differences in clinical opinion
  → unclear how results were used with epidemiological sources to inform proportions
  → **ERG base case uses different distribution of LI and EJ** based on epidemiological evidence and elicited clinical evidence

MLD cohort	Modelled proportions	
	Company base case	ERG base case
PS-LI	XXXX	XXXX
PS-EJ	XXXX	XXXX
ES-EJ	XXXX	XXXX

⊙ ***What proportion of patients in the subgroups are likely to be seen in the NHS?***

BSC transitions between GMFC states

Model transition	LI			EJ		
	Mean time to transition in months					
	OSR-TIGET NHx cohort	Elgun 2019	Kehrer 2011	OSR-TIGET NHx cohort	Elgun 2019	Kehrer 2011
GMFC 0 to 1	XXX	10	10*	XXX	-	-
GMFC 1 to 2	XXX	6	8	XXX	10	27
GMFC 2 to 3	XXX	2	4	XXX	4	2
GMFC 3 to 4	XXX	2	4	XXX	4	2
GMFC 4 to 5	XXX	2	4	XXX	4	2
GMFC 5 to 6	XXX	2	2	XXX	7	12
GMFC 6 to death	XXX	57**	57**	XXX	-	-

*Not reported in trial/publication, used time at entry into GMFC 1 from Elgun as proxy
**Not reported in publication, used value from OTL-200 clinical trial as proxy
***Not based on clinical data. Assumed value to align PS-EJ and ES-EJ cohorts using age and GMFC distribution at treatment from patients in OTL-200 clinical trial

ERG comments

- Generally satisfied with BSC modelling, BUT:
  - "Memoryless" nature of Markov model → previous transitions have no impact on future transitions → predictions do not align with NHx data
  - Short cycle length → patients could progress very quickly (e.g. GMFC 0 to 6 in 6 months) or some are alive into 20s/30s (extremely unlikely)
  - Difficult to ascertain impact → mean time in state can be modelled accurately using Markov model but mistiming of events means discounting and other age/time-related features were not estimated correctly by company

⊙ ***Are the periods that patients stay in each GMFC state typical?***

ERG comments on time spent in GMFC 0 state

- Company modelled time in GMFC 0 is inconsistent with observed data
  - e.g. For EJ: at 103 months, OSR-TIGET patients are in GMFC 5 or 6
- Discrepancies due to data from other natural history studies being used and company made assumptions to increase consistency between PS-EJ and ES-EJ subgroups

- **ERG base case** includes **re-estimation of time spent in GMFC 0** using starting age (as reported by company) and data from OSR-TIGET NHx study
  - Values applied to PS-EJ are also used in ES-EJ

Full responders: GMFC transitions

	Responder, n (%)		
	Full	Partial – stable	Partial – unstable
PS-LI (n = XX)	XXX	XXX	XXX
PS-EJ (n = XX)	XXX	XXX	XXX
ES-EJ (n = XX)	XXX	XXX	XXX

ERG comments

- Full response based on GMFC 0 at last observation BUT not requiring minimum period of stability in GMFC scores
- Some patients classified as partial responders experienced their first decline in function **after more than 24 months follow up**
  - XX patients classified as full responders had **less than 12 months** of GMFC scores recorded (NB: GMFC was not administered until age 18 months)
    → **Scenario analysis** in which patients are classed as stable if in a GMFC state for **at least 12 months**

ERG base case: re-estimated proportion of responders

- Full response required **at least 12 months of stable GMFC scores**
- **Reclassified** patients as **unstable partial responders** if they experienced **a decline after more than 12 months**

ERG

Stable partial responders: GMFC transitions

	Responder, n (%)		
	Full	Partial – stable	Partial – unstable
PS-LI (n = XX)	XX	XX	XX
PS-EJ (n = XX)	XX	XX	XX
ES-EJ (n = XX)	XX	XX	XX

ERG comments

- Company overestimated stable partial responders
- Examples suggest uncertainty in classification
  - some patients show decline in GMFC at latest follow up
  - others show decline after apparent stability → contrary to company's proposed mechanism of action of permanent stabilisation
- Case for late ES-EJ stabilisers appears weaker based on evidence in EPAR that shows slow decline across almost all ES-EJ

→ **ERG base case explores classifying unstable partial response across more ES-EJ patients** (as indicated by trial data)

NICE

ERG

Unstable partial responders: GMFC transitions

	Responder, n (%)		
	Full	Partial – stable	Partial – unstable
PS-LI (n = XX)	XX	XX	XX
PS-EJ (n = XX)	XX	XX	XX
ES-EJ (n = XX)	XX	XX	XX

Progression modifiers applied to partial responders

- Company applied a modifier to each transition from GMFC 0 to 6 to simulate slowed disease progression compared to NHx (based on company clinical expert advice that OTL-200 can slow disease)
  - each GMFC state: progression modifier x natural history time to transition
- **PS-LI and PS-EJ**, 2 approaches to progression modifiers:
  - **Calculation of ratio with NHx cohort** (assumed rate of progression similar irrespective of variant): ratio of average time from GMFC 2 to 5 in OSR-TIGET NHx (combined LI and EJ) and OTL-200 indicated population (combined LI and EJ partial responders → partial responders used to avoid overestimating impact of OTL-200)
  - **Structured expert elicitation (SEE)**: obtained estimations of progression modifiers from experts (scenario analysis)
- **ES-EJ: not possible** to use calculation method because of paucity of data and small sample size → **structured expert elicitation only**

ERG comments on GMFC transitions in unstable partial responders

- Proportions based on trial data are highly uncertain as several response categories are populated by 1 patient
- Unclear which XX patients company used to calculate PS-LI and PS-EJ modifiers
- Most patients in OSR-TIGET NHx cohort had LI MLD (more rapid progression than EJ) → biased progression modifiers in favour of OTL-200
- Only patients (XX with GMFC 2 to 5) with slower disease trajectory from OSR-TIGET study included in calculation:
  - more rapidly progressed patients (GMFC 2 to 6) available but excluded (no recorded GMFC 5)

  → Increased mean state residence times

  → OTL-200 responders with lower rates of cognitive impairment and positive HRQoL for longer vs BSC with high resource use and time in GMFC 5/6 associated with strongly negative utilities → makes OTL-200 look more cost effective
- Published literature (Kehrer 2011 and Elgun 2019) showed significant discrepancies:

MLD subgroup	Time spent in GMFC 5 in months		
	OSR TIGET study	Kehrer 2011	Elgun 2019
LI	XX	2 (n=21)	2 (n=29)
EJ	XX	12 (n=38)	7 (n=32)

ERG base case: same set of progression modifiers for PS-EJ and ES-EJ → justification for accepting key efficacy inputs based on clinical opinion

ERG reclassification of responders

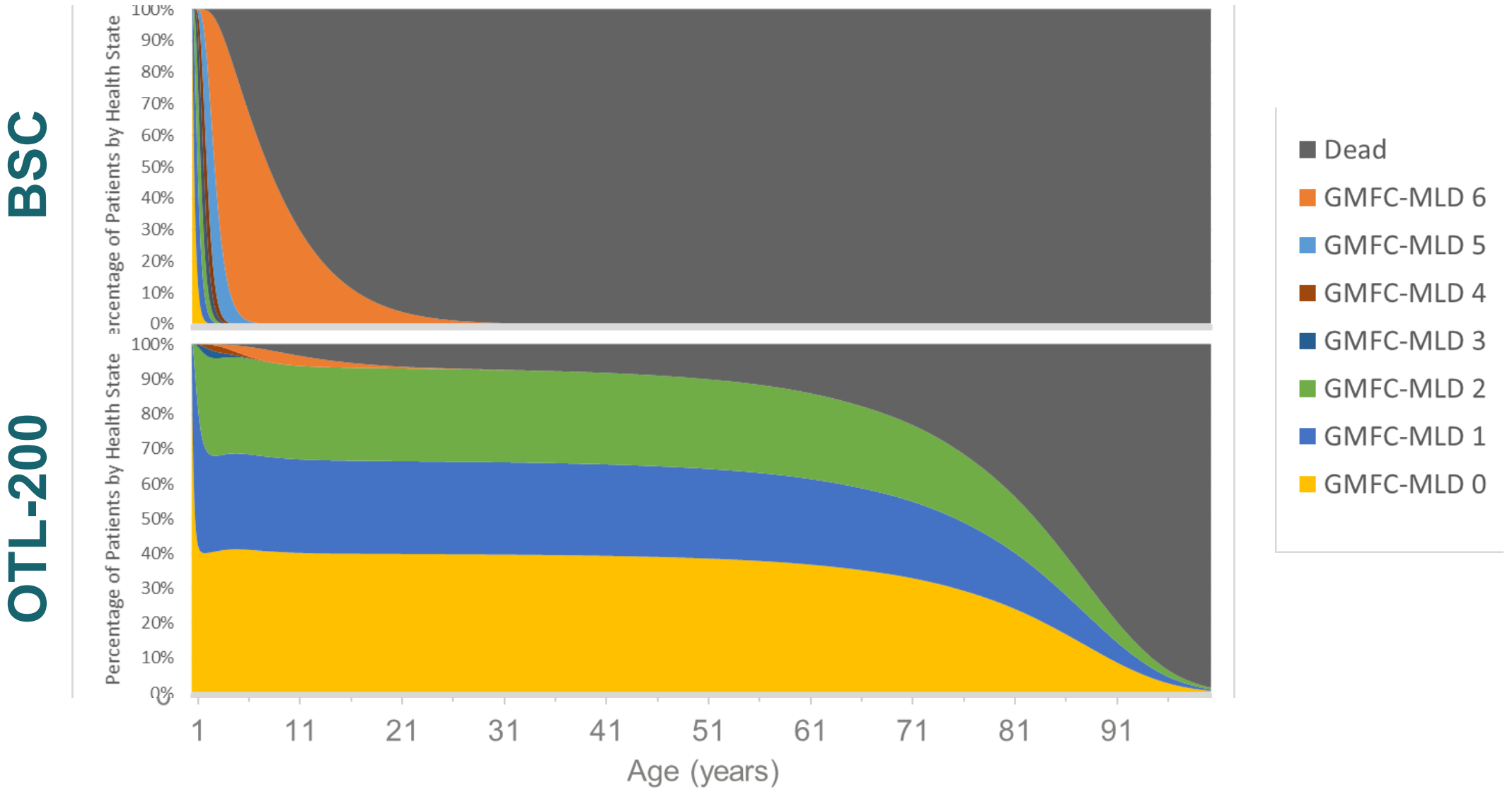
	Responder, n (%)		
	Full	Partial – stable	Partial – unstable
PS-LI (n = XX)	XX	XX	XX
PS-EJ (n = XX)	XX	XX	XX
ES-EJ (n = XX)	XX	XX	XX

ERG reclassification

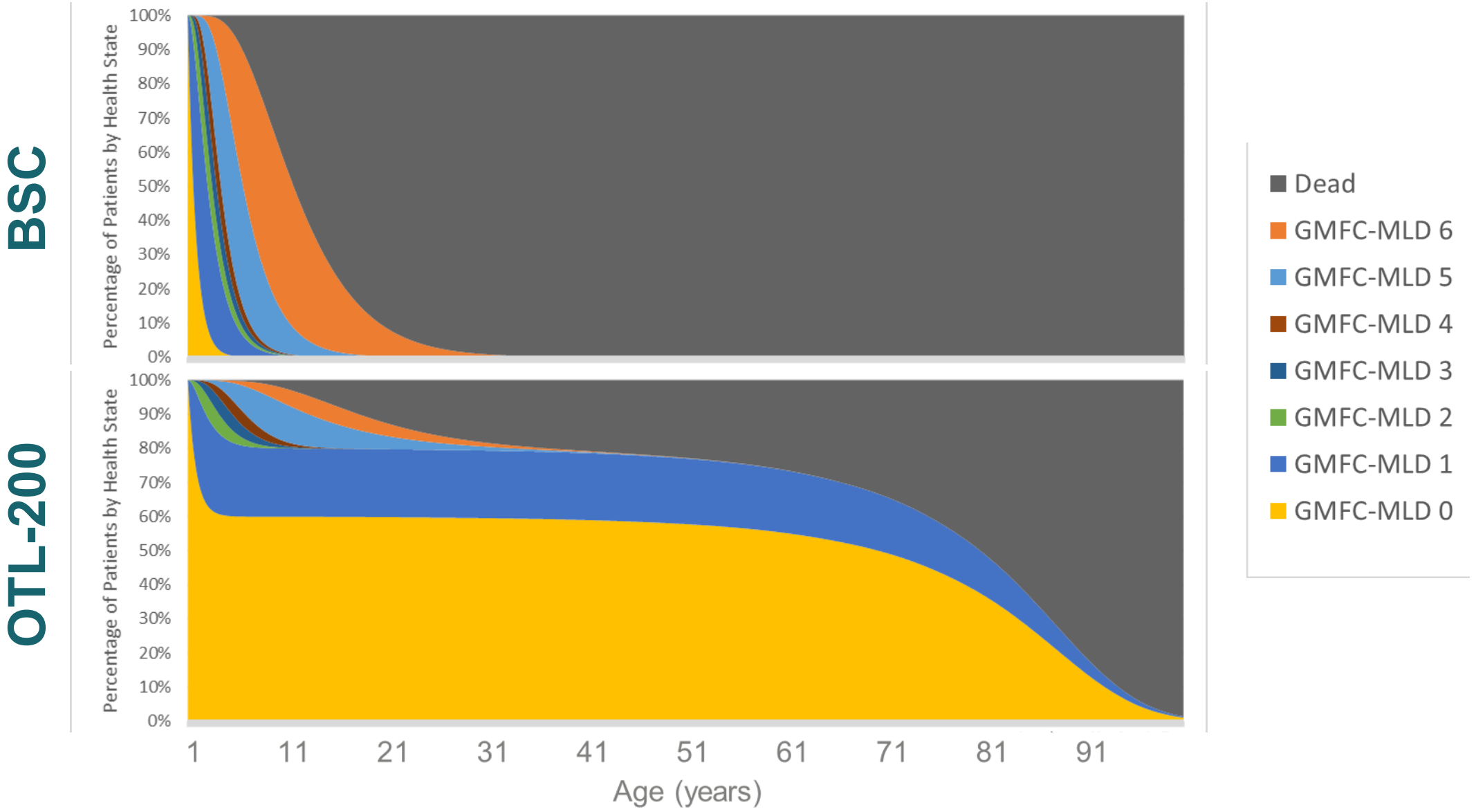
ERG

	Responder, n (%)		
	Full	Partial – stable	Partial – unstable
PS-LI (n = XX) Base case: 2 patients with <12 months follow up are excluded	XX	XX	XX
PS-LI (n = XX) Scenario: patients with <12 months follow up and decline classed as unstable partial responders	XX	XX	XX
PS-EJ (n = XX)	XX	XX	XX
ES-EJ (n = XX)	XX	XX	XX

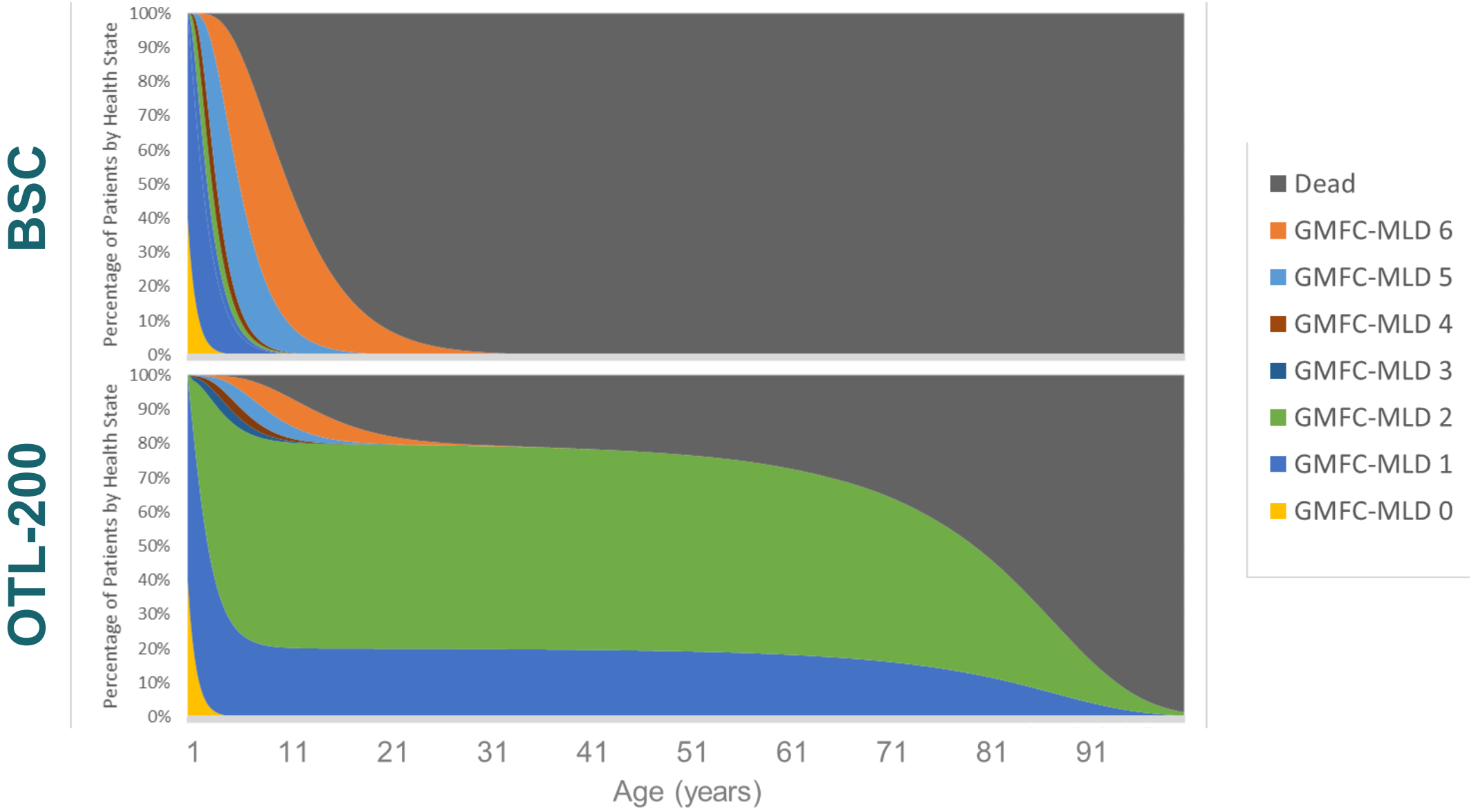
Modelled GMFC output: PS-LI



Modelled GMFC output: PS-EJ

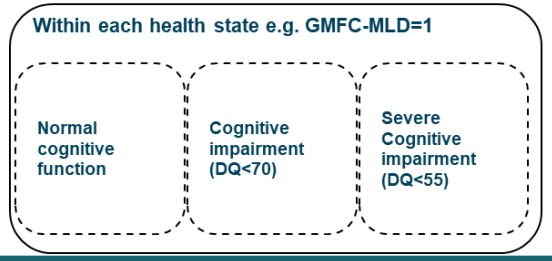


Modelled GMFC output: ES-EJ



Cognitive sub-states – treatment dependent

- **BSC:** Company proportion of moderate and severe cognitive impairment (MCI/SCI) based on clinical elicitation exercise. Cognitive decline broadly aligned with loss of gross motor function
- **OTL-200:** Based on clinical advice, company assumed loss of gross motor function would not necessarily be accompanied by loss of cognitive function. Most patients remain in normal/mild loss sub-state until GMFC 5
- **ERG clinical expert:** cognitive loss could occur before or after motor function decline in MLD



	Cognitive sub-state distribution (impairment level)								
	BSC			OTL-200 full			OTL-200 partial		
	Normal/ mild	MCI	SCI	Normal/ mild	MCI	SCI	Normal/ mild	MCI	SCI
GMFC 0 before cognitive decline	XX	XX	XX	XX	XX	XX	XX	XX	XX
GMFC 0 after cognitive decline	XX	XX	XX	XX	XX	XX	XX	XX	XX
GMFC 1	XX	XX	XX	XX	XX	XX	XX	XX	XX
GMFC 2	XX	XX	XX	XX	XX	XX	XX	XX	XX
GMFC 3	XX	XX	XX	XX	XX	XX	XX	XX	XX
GMFC 4	XX	XX	XX	XX	XX	XX	XX	XX	XX
GMFC 5	XX	XX	XX	XX	XX	XX	XX	XX	XX
GMFC 6	XX	XX	XX	XX	XX	XX	XX	XX	XX
Time until cognitive decline (months)		XX			XX			XX	

ERG comments on cognitive sub-states

- Could not verify source in elicitation report to support assumption that cognitive function is preserved for OTL-200 patients despite deteriorating gross motor function
- Substantial uncertainty with assumption: only possible if protective effect of OTL-200 is more rapidly established in brain than peripheral nervous systems
  - not supported by ARSA activity in CSF: ARSA levels in partial responders did not reach normal reference range until at least 2 years and was only XX at 6 months (compared with XX at 6 months and XX at 1 year for PBMCs)
- Insufficient evidence to support assumption that OTL-200 will have an independent and stronger effect upon brain than wider nervous system

ERG base case: applies same distribution of cognitive sub-states in equivalent GMFC states regardless of treatment received

ERG

⊙ ***Does OTL-200 have a more rapid protective effect in the brain than in the peripheral nervous system?***

Mortality

- Company base case assumes general population levels of all-cause mortality in all states (GMFC 0 to 5) except GMFC 6
- Company used parametric survival analysis of OSR-TIGET cohort to estimate risk of death over time from GMFC 6 with separate curves for LI and EJ patients
  - ERG corrected errors in implementation of this survival analysis (company corrected base case)
  - ERG explored combining LI and EJ data
- Company assumption means no mortality risk from MLD until GMFC 6

	Modelled mean age at death (BSC)	Published mean age at death
PS-LI	XX	4.2 years
PS-EJ	XX	17.4 years
ES-EJ	XX	17.4 years

- Mean age at death calculated by summing BSC mean time to transition values (validated by clinical experts)
- Differences between modelled and published values for PS-LI are likely due to the 57 months OSR-TIGET NHx patients spent in GMFC 6 before death (improved management)

ERG comments on mortality

- Functionally stabilised patients (full and stable partial responders) would have mortality associated with lifelong neurodisability
  - **ERG base case includes standardised mortality ratios for GMFC 1 to 5** informed by values applied HST12 (cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2)
- Appropriate to model 1.25 increase in long-term mortality associated with having undergone myeloablative conditioning (informed by NICE appraisal of betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia)

ERG

GMFC state	MLD-related standardised mortality ratios vs general population (LI and EJ)
GMFC 0	1.25
GMFC 1	1.65
GMFC 2	1.65
GMFC 3	2.25
GMFC 4	2.25
GMFC 5	10.17

Health valuation

Company utility study

- No EQ-5D data collected in OTL-200 studies → company commissioned elicitation study to generate health state utilities (Nafees 2020)
- **Vignettes** (brief list of bullet points) described 24 health states of experiences of:
  - LI (defined using GMFC 1 to 6 only) developed by 3 specialist consultants in metabolic disorders
  - EJ (additionally defined by 3 levels of cognitive impairment) developed by 2 clinicians and a clinical neuropsychologist experienced in assessing cognitive performance in MLD
- **Time trade-off (TTO) interviews** with **general public** for LI (n=100) and EJ (n=101):
  - Participants were asked to imagine experiencing each health state in vignettes and choose from standard TTO choices:
    - A) to live in health state for a period of 10 years followed by death
    - B) to live for X years in full health followed by death (X = 0 to 10 years, changed sequentially until participant is indifferent between Life A and Life B. When Life A was death and participants still preferred Life A, moved to lead-time valuation that asked if 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 vignette) → utility of -1 = participants rather die immediately than live 10 years in full health followed by 10 years in a particular health state
    - C) to indicate that 2 previous options were equally desirable
  - Participants also placed each state (including 'dead') on a **visual analogue scale** (VAS)

Company utility study: Results

- **LI:** values elicited from utility study implemented without adjustment in model
- **EJ:** a linear regression model used to predict EJ utilities based on GMFC and cognitive function
  - **ERG comment:** possibly due to apparent inconsistencies in mean TTO values generated by participants for EJ health states
- Carer disutility: applied in GMFC 5 and 6 for 2 caregivers
- Age adjustment for utility values: only applied in GMFC 0 with no/mild cognitive impairment

Health state	LI	EJ (normal cognition)	EJ (moderate cognitive impairment)	EJ (severe cognitive impairment)
GMFC 0	-	-	XX	XX
GMFC 1	XX	XX	XX	XX
GMFC 2	XX	XX	XX	XX
GMFC 3	XX	XX	XX	XX
GMFC 4	XX	XX	XX	XX
GMFC 5	XX	XX	XX	XX
GMFC 6	XX	XX	XX	XX

ERG

EJ utility values: TTO and regression model

ERG comments

- high level of uncertainty associated with many of the more challenging health states
  - some rated as better than others which company considered 'worse' in regression model
  - utility predicted by regression model for GMFC 6 + severe cognitive impairment was substantially lower than mean TTO value from utility study

Company health evaluation: ERG concerns

- Elicitation exercise: non-reference case approach with insufficient justification
- Results lack face validity
  - Lack external validity compared with utility values used in other appraisals
- Content and construction of vignette descriptions are inconsistent
- Issues with conduct of time-trade off exercise
- Separate, additive impacts of cognitive impairment disutility implemented through the regression model
- Complexity of requiring 2 separate utility value sets for LI and EJ (with cognitive impairment considered)
- Need for correction of age adjustment of utility values across different GMFC states
- Implementation of caregiver quality of life

ERG comments on non-reference case

Valuation approach is inconsistent with NICE reference case

- NICE reference case: QoL data directly from patients using EQ-5D or proxy with experience of condition e.g. caregivers
  - *"if EQ-5D is considered inappropriate then evidence must be provided that it performs poorly in construct validity tests and responsiveness in this population"*
    - Company did not provide evidence of this
- NICE cost-utility analyses: purpose not to directly model public preferences, but to represent patient's own perceived QoL through lens of public preferences using validated tools e.g. EQ-5D
  - Beyond remit of company to generate public preference weights
- Company's value set captures only public preferences with very poor between-participant agreement in many health states, includes no explicit consideration of QoL of patients themselves and lies significantly outside range of established UK EQ-5D preference weights

  → approach taken in HST12 (Cerliponase alfa for late infantile neuronal ceroid lipofuscinosis) may be adequate: 8 clinical experts completed EQ-5D-5L as proxy for patients

Considers utility values elicited through company valuation study are unfit for decision making

ERG comments on face validity

Extent and magnitude of negative utilities in company value set

- Utility for GMFC 6 + severe cognitive impairment ([redacted]) is by far most negative utility applied in NICE appraisal (applied throughout majority of lives in BSC)
- Company's base case: BSC generate [redacted] QALYs ([redacted])
- Comparison of utilities in other disease areas suggests lack of external validity
- Fall well below lowest utility ascribed to worst health state as valued by UK general public
  - UK EQ-5D-3L/5L value set lowest possible value is -0.594

External validity

- Company provided evidence of NICE appraisal with worse than death utilities: most severe level of multiple sclerosis in adults at **-0.195** ("Confined to bed and totally dependent, unable to communicate effectively or eat/swallow" = Expanded Disability Status Scale 9)
- Company summarised survey of caregivers (n=20) reporting impact of MLD on their children's QoL (95% unable to walk)
  - Mean PedsQL (Pediatric Quality of Life Inventory) 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

External validity of negative patient utility values in OTL-200

HST12: Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

- Rare genetic, neurological disease
- Onset 2-4 years (mean life expectancy 10 years)

How health states were defined	Utility values (extremes presented)
CLN2 rating (4 point) scale: • Motor (0=immobile; 3=grossly normal gait) • Language (0=none; 3=grossly normal) **Utility elicitation:** 8 clinical experts completed EQ-5D-5L as proxy for patients (vignettes)	10 health states (HS) (increasing disease severity) HS7: Immobile (-0.358) HS8: Immobile & vision loss (-0.326) HS9: Immobile & vision loss & palliative care (-0.389)

⊙ *Are the company's elicited utilities plausible?*
⊙ *Is the company's valuation study robust for decision making?*

ERG comments on vignettes

Vignettes may not be representative of health states

- **Context of MLD:** unclear if even well-designed vignettes could plausibly equip healthy adults to comprehend life of a child with MLD
  - Company vignettes provided little context e.g. for LI, they did not mention that participants were imagining life of a young child who is likely to still be in early development
- **Incomplete or inaccurate descriptions**
  - descriptions of equivalent GMFC states are inconsistent between LI and EJ e.g. trouble with sight and vision loss sometimes in LI GMFC 2 (permanent in GMFC 3) but not mentioned in EJ → possible large effect on observed utilities of GMFC 2 (XX in LI vs XX in EJ)
  - Neuropsychologist noted that severe cognitive impairment (SCI) is characterised by loss of interest/responsiveness and that 'it is difficult to determine whether children with SCI feel frustration'
    - every vignette of SCI health states described children as feeling 'very frustrated when you are unable to do things…'
- **Inconsistency of results:** evidence participants had difficulty distinguishing between health states leading to some inconsistencies (e.g. participants assigned a higher mean TTO utility to GMFC 2 + SCI (XX) than to GMFC 1 + SCI (XX), and GMFC 6 + SCI was rated better (XX) than GMFC 5 + SCI (XX)

ERG comments on TTO exercise

Time trade off (TTO) methods may be conceptually difficult to understand

- **Time horizon of TTO exercise**
  - Participants asked to imagine being in health state for 10 years after a period of 10 years in full health → possible response bias; unwilling to commit to 10 years of bad health vs 1 year (more appropriate given nature of MLD progression)
- **Patterns of response trend towards best and worst possible health states**
  - TTO exercise resulted in clustering around best and worst possible ratings (-1, 0 and 1) across health states
    - -1 most common response; few responses between -1 and 0
    - 12% of participants' responses too inconsistent and excluded from analysis → difficulty in understanding conceptually demanding and abstract questions
- **Inconsistency between TTO and VAS ranking methods**
  - Participants' ratings of each health state on VAS showed inconsistencies with TTO results
    - 8/18 EJ health states were assigned worse than death utilities using TTO method, same participants ranked only 3 health states as being worse than death on VAS: GMFC 6 + MCI (XX); GMFC 5 + SCI (XX) and GMFC 6 + SCI (XX)
    - Conceptual simplicity of VAS and lower relative standard deviations around each mean value → VAS scores may be better indicator of participants' perceptions of health states

ERG comments on cognitive impairment impact on HRQoL

Substantial effect of cognitive impairment on utility estimates

- Company utilities suggest that child with very limited cognitive function has worse perception of own QoL than child fully aware of condition in later health states
  - ERG's clinical advisor: in MLD, discomfort, pain and some preserved cognitive awareness result in greatest distress at GMFC 4 and 5, before patients become more unresponsive and spend much of their lives asleep in GMFC 6
- Company assumes additive relationship between motor dysfunction and cognitive capacity
  - No evidence. ERG's clinical advisor: not plausible
  - Patients who are already entirely dependent will experience little or no additional impact on perceived HRQoL with increasing cognitive dysfunction. In other disease areas, patients with SCI and complete loss of motor function are considered to have a 'near-death' QoL, with utilities of 0.08 to 0.11 ('persistent vegetative state')

Uses public perceptions of cognitive impairment

- Participants showed clear bias against health states involving cognitive impairment e.g. many participants would rather die immediately than experience cognitive impairment, even after a long period of full health

Large and independent effect of cognitive impairment on modelled utilities for EJ

- Company's regression analysis applied a flat disutility for each tier of cognitive impairment
- OTL-200 patients follow much less severe disease trajectory because of separation of cognitive and motor components

ERG base case: removed cognitive impairment utility decrements (HRQoL determined only by GMFC score, no independent effect of cognitive impairment)

- Additional scenarios to show effect of this assumption

ERG

ERG comments on inconsistency in LI/EJ utilities

LI utility values applied for duration of model

- **Company originally applied EJ utilities from 4 years**
  - Unrealistic jumps in utilities (e.g. GMFC 2 ([redacted]) and GMFC 3 ([redacted]))
    - Company applied LI utility for entire time horizon
  - ERG considers that in theory, utilities generated for EJ patients would be more representative of older LI patients with MLD
- Application of 2 separate utility sets is overly complex and unnecessary

ERG base case: EJ utility value set applied to LI population

- Additional scenarios with LI utility values applied to EJ population

ERG comments on age-adjusted utilities

Company approach only adjusted utilities as patients aged in GMFC 0 with normal cognition/mild impairment

- Patients with moderate cognitive impairment have same utility value at 76 years as patients with normal cognitive function for rest of time horizon
- Patients who stabilised in GMFC 1 had higher utility than patients stabilised in GMFC 0 at 36 years+ and those who stabilise in GMFC 2 at 56 years+

  → ERG considers there is no reason that HRQoL of these patients will not decline in line with rest of population
- Inappropriate use of predictive equation (Ara and Brazier)

  → leads to assumption that HRQoL peaks at birth (using utility derived from adults) and deteriorates from 1 year

ERG base case: corrects use of predictive equation and **applied to all patients regardless of GMFC values**

ERG

ERG comments on caregiver quality of life

- **Disutility values obtained from survey:** 21 caregivers completed EQ-5D-5L (6 UK based; Pang 2020) → disutility of **-0.108** from anxiety and depression (71%) and pain/discomfort (62%)
- **Company base case: no caregivers are needed until GMFC 5** (based on advisory board report), at which point 2 caregivers are needed, both of whom incur disutility (**total -0.216**)
- **Applying caregiver disutilities only in GMFC 5 and 6 is inappropriate**
  - ERG clinical advisor suggests that full time care and supervision is needed from at least 1 parent from GMFC 2 (estimated 15 hours caring per day)

Health state	Number of caregivers required	
	Company base case	ERG base case
GMFC 0	0	0
GMFC 1	0	0.5
GMFC 2	0	1
GMFC 3	0	1
GMFC 4	0	2
GMFC 5	2	2
GMFC 6	2	2

ERG

ERG base case: different distribution of caregivers

⊙ ***Which distribution of caregivers in the different health states reflect patient experience?***

Costs, resource use and discounting

Treatment costs

Items	Value	Source
OTL-200	£2,875,000	List price
Leukapheresis (cell harvest)	£4,272	Weighted average of Healthcare Resource Groups (HRG) for stem cell (SA34Z) and bone marrow harvest (SA18Z)
Conditioning	£7,899	HRG for paediatric metabolic disorders hospitalisation non-elective inpatients (weighted average cost = £7,761) + cost of busulfan
Administration and hospitalisation	£24,188	• HRG paediatric metabolic disorders admissions weighted average elective inpatient – calculated for 11 days (weighted average cost = £5,068) • SmPC states patient would stay about 4 – 12 weeks (average of 7.5 weeks) extension of an additional 41.5 days (weighted average cost = £19,120)
Follow-up transplant costs	£61,965	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	£2,973,324	Calculation based on list price

ERG comments on treatment costs

Generally lacking in detail, small but important aspects of treatment pathway are not appropriately costed BUT small proportional cost means ERG did not explored

Some specific administration cost concerns:

- **Screened patients who do not receive OTL-200:** unclear if NHS would incur OTL-200 costs of patients screened but who do not receive OTL-200
- **Initial costs of screening:** not included
- **Costs of conditioning:** costs of clinical laboratory and monitoring tests, prophylaxis of seizures and VOD (veno-occlusive disease) during conditioning
- **Missing adverse events costs:** 69% of trial patients had a serious AE that could require excess bed-day HRG cost
- **Inappropriate transplant and post-transplant costs:** cost of alternative HRG code (Peripheral Blood Stem Cell Transplant, Autologous, Code SA26B) is more appropriate → £34,539 per episode vs company's £24,188 per episode
- **Cost of monitoring and treating patients for 2 years after treatment with OTL-200: costs** overestimated as company based on an NHS Blood and Transplant analysis for patients with leukaemia receiving an unrelated adult donor transplant in the Netherlands from 1994 to 1999 → limited relevance

⊙ ***Should screening costs be included in the model?***
⊙ ***What proportion of patients screened would likely be ineligible for treatment with OTL-200?***

Health state costs

- No relevant resource use studies
- Company conducted an elicitation exercise to estimate health care resource use (HCRU):
  - **opinion from 5 clinical experts** on frequency, duration and proportion of HCRU for MLD UK patients, including medical visits and equipment use, social caregiver use for each GMFC state
  - where no response provided, **views from an Italian clinician with direct experience of treating patients** with OTL-200 were used
- Majority of health state costs come from hospitalisation costs and social care costs
- From GMFC 4 to 6: all patients need support from a social care professional to provide enteral nutrition support for 8 hours per day for 292 days annually
- GMFC 5 and 6 (including permanently hospitalised patients): additional social care costs for other care needs

Resource use in GMFC 0

- **Full responders in GMFC 0 are assumed to have at least 1 annual monitoring visit for 18 years after treatment with OTL-200**
  - Reflects SmPC: patients should be monitored for signs of leukaemia or lymphoma during routine yearly check ups and monitoring for anti-ARSA antibodies up to 15 years post treatment
  - Company assumes any other costs are captured in 2-year post-treatment follow-up transplant costs
- **ERG considers other costs associated with a full response**
  - GMFC scores may be overly simplistic and fail to capture other manifestations of MLD which may be treated sub-optimally by OTL-200 (e.g. peripheral neuropathy)
  - ERG clinical advisor: possible neuropathic pain in fingers and legs, paraesthesia and loss in fine motor skills
  - Patients may still prefer using walking aids or wheelchairs at GMFC 0
  - Patients classified as functionally stabilised may continue to experience manifestations of MLD such as hepatobiliary disorders, metabolic acidosis, and renal tubular acidosis resulting in additional costs to NHS
- **No additional scenarios presented**
  - Difficult to establish long-term care needs of patients given limited data and clinical experience of using gene therapies

Resource use applied to patients with late stage disease

- **In GMFC 6, company assumes that 20% are cared for in hospital or hospice full time**
  - ERG clinical advisor: residential hospitalisation is extremely rare; used for resolving specific medical needs such as status epilepticus, gastrostomy fitting, or to treat a serious infection
    - Already included in hospitalisation costs for patients cared for at home
  - Company derived costs from acute care setting (i.e. hospitalisation) and not chronic care (i.e. hospice) setting → overestimated costs
- **Company assumes that hospitalised patients also receive an additional 7.2 hours of social care provision per day for 292 days of the year**
  - ERG clinical advisor: social care support would not be routinely given except in certain circumstances (single parent household) or if there was change in care needs (e.g. overnight supervision of respiratory needs)
- **Combination of these factors results in care costs of patients being estimated to be over £800 per day in hospitalised patients**
  - Lacks face validity
  - Daily costs in cerliponase alfa in HST12 are substantially lower

ERG

- **ERG base case: all patients are cared for at home**
- Additional scenario: **costs of 20% patients in GMFC 6 in hospital full-time removed**

Resource use in adults with symptomatic MLD

- **Model predicts many patients will survive into adulthood → resource use for adult patients will not be equivalent to children**
  - Costs of social care may increase significantly as patients enter adulthood and less able to rely on family members for care needs
  - ERG clinical advisor: From GMFC 2, adults will need some degree of care from social services and from GMFC 3, patients will not be able to live independently and would need significant in-home assistance or institutional care
- **Company provided revised health state costs from 18 years+**
  - PSSRU cost of local authority own-provision care home for adults requiring physical support is £989 per resident week (from HST12)
    - Costs outdated; social services and hospitalisation needs in more severe health states not adjusted for inflation (i.e. daily hospitalisation or support for enteral nutrition)

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%

ERG base case: residential social care provision with PSSRU costs

- Residential care: £1272 per week
- Day care: £245 per week

ERG

Discount rate: non-reference case

NICE Methods Guide 6.2.19: "*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. Further, the Appraisal Committee will need to be satisfied that the **introduction of the technology does not commit the NHS to significant irrecoverable costs**.*"

Company considers these criteria are met and use 1.5% discount rate:

- Most OTL-200 patients stabilised in GMFC 0, 1 and 2 with normal/mild cognitive function (utility values for these health states range from XX to XX)
- NHx controls over similar period were in end-stage disease or had died
- Sustained over full lifetime of patients

ERG base case: removes non-reference case discounting; uses 3.5% ERG

ERG comments on non-reference discounting

OTL-200 related **costs are accrued upfront, benefits are accrued over long period of time**

- **Uncertain if OTL-200 returns patients to full or near to full health**
  - Company base case: XX PS-LI XX PS-EJ and XX ES-EJ are classed as full responders. All remaining patients assumed to stabilise in GMFC 1 or 2 or exhibit slowed disease progression. ERG disagrees that GMFC 1 and 2 represent near-normal health
- **Uncertain if OTL-200 acts over a long period of time (over 30 years)**
  - Significant uncertainty whether disease stabilisation is permanent. Durable clinical efficacy is seen up to 60 months in XX patients, with a maximum follow up of 77 months (no data beyond this; median XX months). Surrogate markers show evidence of decline
- **OTL-200 will commit NHS to significant irrecoverable costs**
  - Substantial upfront acquisition costs associated with OTL-200 would not be recovered by NHS if engraftment fails at any point
    - Limited long-term evidence of graft durability or stability of GMFC
    - Reductions in benefits and increased care costs may be particularly acute if progression is very slow resulting in patients staying in health states associated with very low or negative HRQoL and very large ongoing care costs
  - Unclear if NHS would incur OTL-200 cost for patients who were eligible at screening but who deteriorated and became ineligible after product was produced at OSR-TIGET

- ***Are treatment effects maintained over a long-period?***
- ***Does OTL-200 treatment return patients to full or near full health (address all aspects of disease)?***
- ***Is it likely that OTL-200 will commit the NHS to significant irrecoverable costs?***

Innovation and equality issues

- OTL-200 represents a step change in management of MLD (disease modifying treatment)

- No equality issues identified by company or ERG

- Lead team have identified potential differential access based on:
  - cognitive function (i.e. IQ requirement)
  - age of treatment (early onset requirement)

⊙ ***Is OTL-200 innovative? Are there any benefits not captured in QALYs?***
⊙ ***Are there any equality issues to consider in particular, in applying the marketing authorisation of OTL-200 and access for people with protected characteristics?***

Key issues: cost effectiveness

- What duration of stable response is sufficient to classify patients as long-term responders?
  - Is the treatment effect in responders sustained life-long?
  - Does OTL-200 protect cognitive function in patients who have motor function decline on treatment?
- Are the utility values applied by either the company or the ERG valid for decision making?
- Is it appropriate to apply non-reference or differential discounting?
  - Is the judgement regarding the appropriate discounting rates different?
- Are the subgroups clearly defined to allow for separate recommendations to be implemented in clinical practice?
  - Is the balance of costs and benefits different for the PS-LI, PS-EJ and ES-EJ subgroups?
  - Is the uncertainty around the ICER estimates greater for any of these groups?
  - Is the QALY weighting (based on undiscounted QALYs gained) higher or lower for any of these groups?

ERG base case assumptions

ERG

Model structure and inputs	**Cognitive decline linked to GMFC progression OTL-200 patients**	Moderate
	Alternative MLD subgroup distribution	?
	Discount rate of 3.5% for costs and benefits	Major
	Patients with <12 months follow up excluded	Major
	Equivalent progression modifiers applied in ES EJ and PS EJ	Minimal
	Re-analysis of OSR-TIGET health state residence times	Minimal
Mortality	Incorporation of neuro-disability-related and myeloablative conditioning SMRs for patients in GMFC 1-5	Minimal
	Updated survival models based on pooled LI/EJ data in GMFC 6	Minimal
HRQoL and utility values	QoL based on GMFC only (no independent cognitive effect)	Minimal
	EJ utilities applied to LI	Minimal
	Age adjustments removed from patients aged <16 and applied to all patients regardless of GMFC	Minimal
	Caregiver decrements applied at an earlier stage of disease	Moderate
Resource use	Assume all patients in GMFC 6 are cared primarily at home	Minimal
	Adult social care costs include institutional care	Minimal
Sensitivity of stabilisation	**Stability persists for 50 years on average**	Major
	Stability persists for 20 years on average	Major
	Stability persists for 10 years on average	Major

NICE

Effect on pooled ICER: Minimal <10% effect, Moderate 10%-20%, Major >20%
? Minimal effect on company base case; major effect on ERG base case

Cost-effectiveness results to be discussed in Part 2