NICE National Institute for Health and Care Excellence

Version for PUBLIC – contains no ACIC information

ID1666 OTL-200 for metachromatic leukodystrophy

Chair's presentation

2nd HST committee meeting

Chair: Paul Arundel

Lead team: Matt Smith, Sarah Davis, Mark Sheehan

ERG: York (Centre for Reviews and Dissemination and Centre for Health Economics)

Technical team: Sharlene Ting, Adam Brooke, Nicole Elliott

10th June 2021

Background

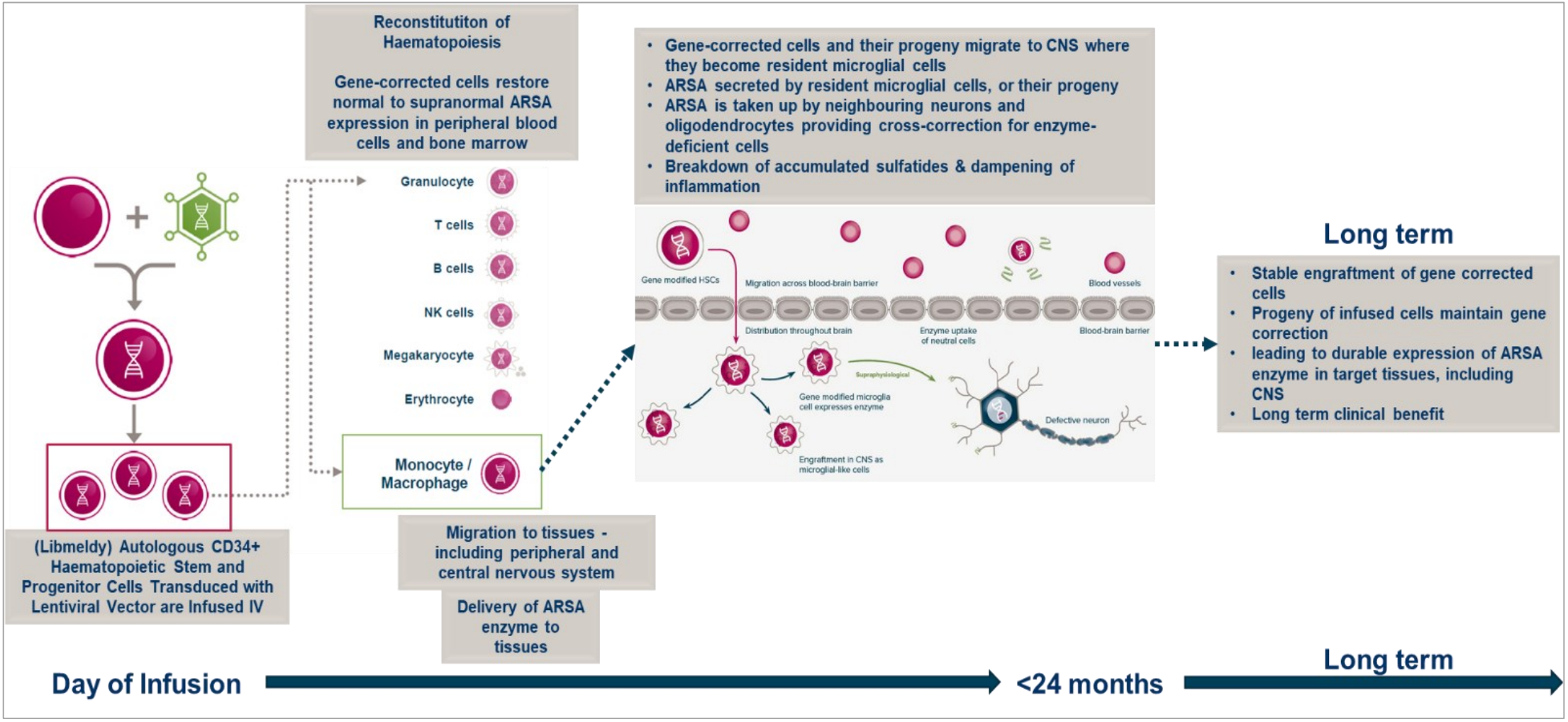
Metachromatic leukodystrophy (MLD)

- Rare hereditary disease → unable to breakdown sulphatides → accumulation → destroys myelin sheath around nerves
- Clinical course: pre-symptomatic stage (normal motor and cognitive development) → developmental plateau → early onset of first symptoms (early symptomatic) → rapid and predictable trajectory of progression (loss of abilities in motor function, language and cognition leading to premature death)
- Birth prevalence: about 4–5 babies with MLD every year in England and Wales

OTL-200

- Marketing authorisation: treatment of MLD characterised by biallelic mutations in arylsulphatase A (ARSA) gene leading to decreased ARSA activity:
  - in children with **late infantile (LI) or early juvenile (EJ) forms, without clinical manifestations** of disease **(pre-symptomatic, PS)**
  - in children with **early juvenile form, with early clinical manifestations** of disease, who can walk independently and before onset of cognitive decline **(early symptomatic, ES)**

Mechanism of action of OTL-200



Company: on successful engraftment, OTL-200 works to re-populate 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**'

Decision problem

	Company submission	Committee considerations
Population	In line with marketing authorisation (PS-LI, PS-EJ and ES-EJ)	Identification of "early symptomatic" EJ: IQ ≥85 and GMFC 0 or 1
Intervention	OTL-200 (fresh and cryopreserved formulations)	• Company's economic model uses OTL-200-fresh evidence only • OTL-200-cryopreserved used commercially but limited evidence of comparability
Comparator	Natural history cohort (best supportive care): 19 LI, 12 EJ	• Allogeneic haematopoietic stem cell transplantation (HSCT) not relevant • Natural history cohort: no individual patient matching. Matched sibling analysis (limited numbers, n=11)
Outcomes	• ARSA activity (CSF, PBMC) • Gross motor function (GMFM, GMFC) • Developmental quotient (DQ) • Nerve conduction velocity (NCV)	Health-related quality of life not assessed in OTL-200 studies

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

- XX patients with PS-LI
- X patients with PS-EJ
- X patients with ES-EJ

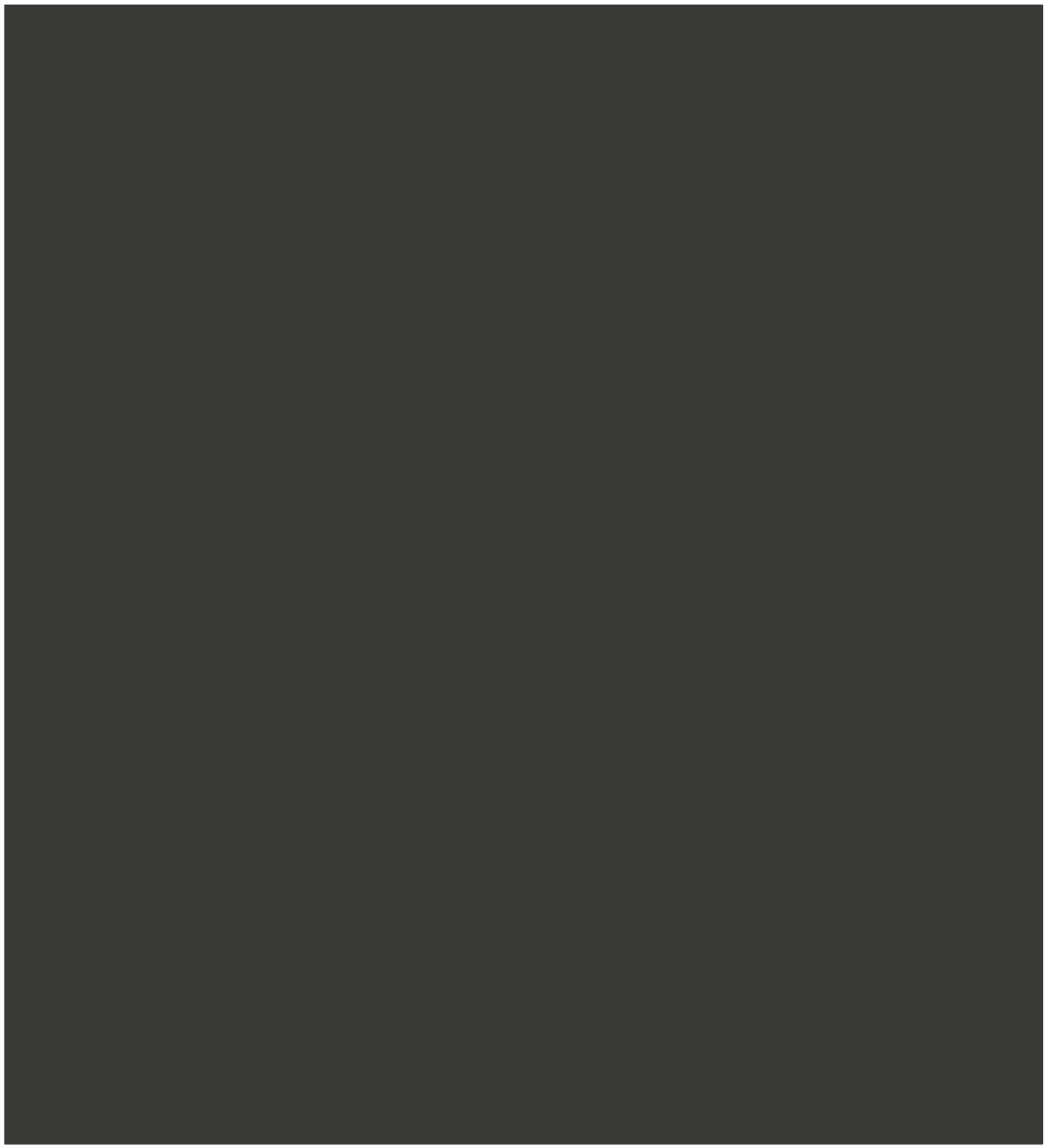
Gross motor function outcome measures

Company used 2 assessment tools to measure gross motor function:

- **GMFM**: 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

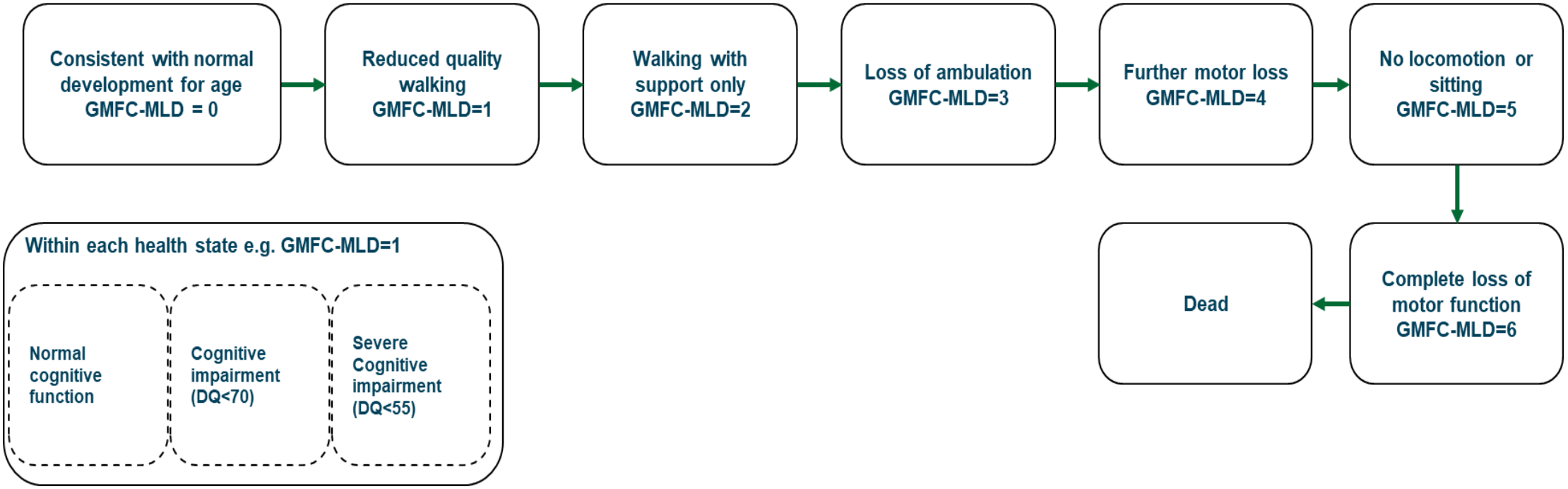
GMFC panel plots in PS-LI and EJ (PS and ES)



PS-LI patients

EJ (PS and ES) patients

Company original 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 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 original OTL-200 response classification

Company modelled 3 categories of response for OTL-200

- **Full responders:** patients treated before symptom onset, 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 then stabilise, **or** patients who have some progression after treatment but then stabilise in GMFC 1 or 2 (based on trial data and clinical expert opinion)
- **Unstable partial responders:** patients in whom OTL-200 has failed to stabilise progression. Patients progress through GMFC states but at a slower rate than BSC (calculated compared to NHx cohort and expert elicitation)

ERG comments

- **Uncertainty about durability of response and final health state:** small numbers and limited follow up especially in ES-EJ subgroup
- **ARSA activity in CSF:** unclear relationship between ARSA activity and clinical outcomes over long term
- **Variability in direction of clinical outcomes:** NCV show possible signs of progression
- 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

After first committee meeting

Committee considerations	Company	Slides (TBC)
Limited evidence and uncertainty about treatment response categorisation	New data cut (dated May 2021, follow-up visits until December 2019): ~2 years additional data on 17 patients	12-28
Uncertainty about effectiveness in ES-EJ subgroup	New data cut and scenario analyses: • Adjusted progression modifiers applied to ES-EJ • Updated distribution of stabilisation states	18-35
Uncertainty about stabilisation / durability of treatment response	New data cut and scenario analysis	29-32
Distribution of subgroups	No new evidence	36
Credibility of utility set	Revised utility set and evidence supporting quality of life benefits from OTL-200 treatment	37-41
Limited evidence on OTL-200 cryopreserved formulation	No new evidence – data for similar analogues	-
Other	Updated patient access scheme	-

Updated evidence and analysis after ECM1

New data cut for fresh formulation only

Company provided data for visits up to December 2019 (data cut May 2021):

- ~2 years' of data on 17 patients: 8 PS-LI, 4 PS-EJ, 5 ES-EJ
- ≥5 years of follow-up for patients in **registrational trial and CUP 207394**

ERG comments

- Company provided no statistical analyses of data, only figures → ERG provided summary of changes in key outcomes per patient
- Continuing pattern of decline in many partial responders, with far fewer patients achieving long-term stabilisation → **company's original revised base case** most likely reflects pattern of response observed in OTL-200 patients (see next slide)

Since last data cut	PS-LI (n=X)	PS-EJ (n=X)	ES-EJ (n=X)
Decline in GMFC and GMFM **ERG:** Patients may stabilise for 2-3 years before further decline in GMFC → **stabilisation assumptions uncertain** → increases burden of proof to establish stability in specific patients	X	X	X
Decline in cognitive function (DQ) **ERG: High within-patient variability** makes interpretation difficult	X	X	X
Decline in ARSA activity in CSF (near or below minimum level for healthy adults 0.31nmol/mg/h and below 0.71nmol/mg/h threshold level EMA suggests may show treatment effect in LI)	X	X	X

ERG

Classification of treatment response

Subtype	Response category	Company base case		ERG base case	
		Original	Revised	Original	Revised
PS-LI	Full	[redacted]	[redacted]	[redacted]	[redacted]
	Stable partial	[redacted]	[redacted]	[redacted]	[redacted]
	Unstable partial	[redacted]	[redacted]	[redacted]	[redacted]
PS-EJ	Full	[redacted]	[redacted]	[redacted]	[redacted]
	Stable partial	[redacted]	[redacted]	[redacted]	[redacted]
	Unstable partial	[redacted]	[redacted]	[redacted]	[redacted]
ES-EJ	Full	[redacted]	[redacted]	[redacted]	[redacted]
	Stable partial	[redacted]	[redacted]	[redacted]	[redacted]
	Unstable partial	[redacted]	[redacted]	[redacted]	[redacted]

Company 'stable': only if stabilisation occurs across all relevant clinical outcomes and disease markers (previously only based on GMFC score)

ERG classification criteria: i) full responders remain in GMFC 0 throughout follow up and to have at least 12 months follow up, ii) stable partial responders show decline in GMFC only within 12 months of treatment

⊙ ***For ES-EJ subgroup, should all 5 patients be classified as unstable partial responders?***

Company updated classification for stabilisation

- MLD affects all systems → updated classification based on all relevant clinical outcomes (GMFC, GMFM, DQ) and disease markers (MRI and NCV)
- Disease progression: worsening in motor impairment or cognitive function
  - **Progression of motor impairment**: worsening of GMFC and GMFM total score
    - If patient had a drop in only GMFC score but GMFM total score remained stable and other disease markers (MRI and NCV) also remained stable, then patient was assumed to be stable
  - **Progression of cognitive impairment**: defined as an unreversed categorical change in DQ performance i.e. patient goes from normal (>85) to mild (70 – 85) to account for DQ fluctuations

- **Full responders**: motor and cognitive function remained stable throughout follow-up period
- **Stable partial responders**: any patients whose motor and cognitive function appear to have stabilised after an initial period of worsening. To determine GMFC level stabilised at, consider GMFC score where the following:
  - DQ, MRI and NCV should have stabilised or continue to improve for 12 months
  - GMFM total score is stabilising
- **Unstable partial responders**: any patients who show a consistent trend of worsening in motor (GMFM and GMFC) and/or cognitive function

Individual patient profiles

1 PS-LI patient

5 ES-EJ patients

Discrepancies in response classification

	Company base case		ERG base case	
	Original	Revised	Original	Revised
PS-LI				
PS-EJ				
ES-EJ				

*No new data

PS-LI

Response classification	
Company	Full
ERG	Unstable partial

Company: GMFC decline to 1 but GMFM, MRI, NCV and DQ scores all remained stable or continued to improve

NICE

⊙ ***Should MLD-03 be classified as a 'full responder' or an 'unstable partial responder'?***

Response classification	
Company	Unstable partial
ERG	

Response classification	
Company	Stable partial response in GMFC 4
ERG	Unstable partial

Response classification	
Company	Stable partial response in GMFC 3
ERG	Unstable partial

Response classification	
Company	Unstable partial
ERG	

Response classification	
Company	Stable partial response in GMFC 1
ERG	Unstable partial

ES-EJ patient characteristics

ERG noted 2 ES-EJ patients (MLD-13, MLD-14) had been treated at [redacted] and [redacted] years and was unclear how diagnoses were made given patients had [redacted] and [redacted] at treatment

Phenotypic type	Age of symptom onset	Genotype
LI	up to 30 months	2 null alleles (0/0 genotype)
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)

Company

- Confirmed patients were diagnosed before 6 years
- Provided details of genotype consisting of 1 null allele ([redacted]) and 1 residual allele ([redacted])

ERG

- Accepts company clarification but unclear if patients are representative of EJ
- Disease course may resemble Late Juvenile form (slow progression of symptoms over long period of time relative to natural history cohort) → unclear comparability of trial, NHx datasets, and general population of ES-EJ

Response classification	
Company	Stable partial response in GMFC 4
ERG	Unstable partial

[redacted]

Response classification	
Company	Stable partial response in GMFC 3
ERG	Unstable partial

NICE

⊙ *Is the clinical course of MLD-14 typical of early or late juvenile MLD?*

Excluded individual patient profiles

2 ES-EJ patients

Response classification	
Company	Excluded
ERG	Unstable partial

ERG comment: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. Should be included

⊙ ***Should XXXX be excluded from the analysis?***

Excluded ES-EJ patient

ERG comment: patient was excluded due to low IQ. But borderline XXXX at time of treatment, patient had little follow-up data

⊙ ***How would patients in the NHS be identified and assessed for eligibility of OTL-200, in particular with respect to 'early symptomatic' status (e.g. IQ threshold ≥85)?***

Further evidence for stabilisation

Long-term stabilisation: Company comments

- **Mechanism of action of OTL-200 supports long-term stabilisation** greater than 20 years
  - Ex vivo technology uses a retroviral vector such that corrected gene integrates directly into target cell's genome, where it can be replicated whenever the cell divides or differentiates
  - Self-renewal capability of HSPCs suggests when gene-corrected HSPCs successfully engraft in the brain, there would be a steady supply of genetically corrected cells and their progenies for patient's lifetime
- Strimvelis for ADA-SCID showed 100% long-term survival for treated patients
- OTL-200 is broadly based on principle of allogenic haematopoietic stem cell transplants (HSCT) which have shown ongoing durability of effect for metabolic patients beyond 30 years (supported by experienced UK clinical experts in HSCT procedures)
  - HSCT has been used for over 50 years to treat patients with several diseases and has shown to be effective in preventing disease progression
  - **New alternative base case assumes 50 years of stabilisation**

Long-term stabilisation: ERG comments

- Company provided commentary on stabilisation in other conditions → **ERG considers stabilisation should be based on OTL-200 evidence; cannot reliably be inferred from technologies used in other conditions**
- Latest data cut shows decline in GMFC after periods of stabilisation (2-3 years) → unclear if any patient will have long-term stabilisation, or the level of impairment at stabilisation
- **Long-term follow up needed to show stabilisation**, with ≥ 3 years of no decline in GMFC
  - Only 1 patient ([redacted]) had GMFC decline and >3 years follow up
  - Decline in GMFC observed in 1 patient ([redacted]) after ~7 years of stability and no previous evidence of decline → decline can occur after long periods (decades)
- Given latest data cut that suggests patients lose stability and/or continue to decline → **inappropriate to assume lifetime or very long-term stabilisation** based on equivalence with other technologies which have demonstrated long-term effectiveness
- New data has increased concerns about **declining ARSA activity in CSF**. ARSA activity in PS-LI continues to decline (on average, at lower limit of reference range for healthy adults)
- Company states that "… it is normal, physiologically, for CSF enzyme levels to fluctuate between samples…" → no evidence of such fluctuation. Within-patient levels of ARSA show consistent decline in most patients with declining levels. If ARSA levels were fluctuating within normal range, some patients should have higher than average levels; there were none → ERG does not consider that fluctuating measurements is a valid explanation for low levels of activity in many patients

ARSA activity in CSF

- ***How should continued decline of ARSA in CSF be interpreted? What is the rationale for all ES-EJ patients showing above normal levels in ARSA activity in PB despite decline in clinical outcomes?***

Distribution of stabilisation health states in ES-EJ

Company

- Updated distribution of GMFC states over which ES-EJ patients stabilise: XX stabilise in GMFC 1, XX stabilise in GMFC 3 and XX in GMFC 4
- Implausible that **all** ES-EJ patients would stabilise at GMFC 4 → data suggests when treatment effect is established (~6 months to ~2 years), stabilisation seen in all relevant clinical outcomes

ERG comments

- Appropriate to consider ES-EJ based on evidence from new data cut
- **Assumes no further progression will occur** → may not be reasonable given limited follow up and evidence of declining GMFC after several years of apparent stability
- Small numbers (n=X in company base case) mean **assumed distribution is unlikely to be representative of reality.** Distribution of patients stabilising only in GMFC 1, 3 or 4 is unrealistic as patients likely to be distributed across all states, GMFC 1-4
- These assumptions do not impact ERG revised base case because all ES-EJ are considered unstable partial responders → not explored further

Other modelling changes

Progression modifiers for ES-EJ

Company

- Calculated progression modifiers for ES-EJ patients who had disease progression based on new data (previously based on expert clinical opinion)
- XX ES-EJ progressed between GMFC 2 and 3: average time to progression XX months (XX times longer than natural history cohort)
- Noted that in ERG corrected model, progression modifiers for OTL-200 treated ES-EJ patients between GMFC 0-1 and GMFC 1-2 were set at XX and XX respectively → clinically implausible for patients treated with OTL-200 to progress faster than natural history cohort → company set progression modifiers <1.0 to 1.0 in ERG model

ERG comments

- Cannot fully verify methods used to generate progression modifier
- Disease course of some ES-EJ patients may resemble Late Juvenile form → effect on modelled progression modifiers may mean these multipliers do not adequately represent relative progression of MLD
- Considers that there is limited justification to apply different progression modifiers across different MLD subgroups given limited available evidence → new progression scenarios reduce ICER by ~£30,000 per QALY

Modelled population: distribution of subgroups

- Distribution of modelled MLD variants is used to pool the ICERs by expected population

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

Company

- **Accepts ERG base case distribution in their alternative base case**
- Notes difficulty in diagnosing ES-EJ in time to be treated in children without affected siblings
- Considers proportion of ES-EJ will reduce over time as awareness of MLD increases
  → provides 2 scenarios using 1) ERG's distribution of MLD sub-types and 2) company's base case estimates

⊙ ***Which proportion of ES-EJ patients is more plausible? What proportion of ES-EJ patients would be eligible for treatment with OTL-200 without an affected sibling?***

Updated utility values

Utility value set

Company

- No EQ-5D data collected in OTL-200 studies → company commissioned elicitation study to generate health state utilities (Nafees 2020)

Committee considerations

- Elicitation exercise used a non-reference case approach with insufficient justification
- Results lacked face validity and external validity compared to utility values from other similar diseases

Company

- Feedback from clinical experts suggest MLD is considered more severe than other conditions e.g. CLN2 and SMA → company utility approaches are conservative
- QoL benefits (e.g. fewer seizures, less pain, improved cognitive function and feeding) were indirectly captured through differences in distribution of patients across cognitive substates for OTL-200 patients vs natural history patients
  - To address ERG's concerns about high cognitive utility decrement, company presents 2 scenarios
    - Alternative utility set 1 – regression analysis results for rescaled utility set provided to NICE on 14th April 2021 based on UK EQ-5D floor value
    - Alternative utility set 2 – incorporate a utility 'top-up' for cognitive benefits based on CLN2 utility values used in HST12

Utility sets for EJ

Health states	Company original set	Set 1: Company rescaled TTO utilities	Set 2: Company base case 'top up' set (OTL-200)		ERG base case
			Natural history	OTL-200	
GMFC1 + NC	XXX	XXX	0.90	0.90	XXX
GMFC2 + NC	XXX	XXX	0.82	0.82	XXX
GMFC3 + NC	XXX	XXX	0.43	0.71 (+0.276)	XXX
GMFC4 + NC	XXX	XXX	0.12	0.40 (+0.276)	XXX
GMFC5 + NC	XXX	XXX	0.05	0.33 (+0.276)	XXX
GMFC6 + NC	XXX	XXX	0.01	0.29 (+0.276)	XXX
GMFC0 + MCI	XXX	XXX			-
GMFC1 + MCI	XXX	XXX			-
GMFC2 + MCI	XXX	XXX			-
GMFC3 + MCI	XXX	XXX			-
GMFC4 + MCI	XXX	XXX			-
GMFC5 + MCI	XXX	XXX			-
GMFC6 + MCI	XXX	XXX			-
GMFC0 + SCI	XXX	XXX			-
GMFC1 + SCI	XXX	XXX			-
GMFC2 + SCI	XXX	XXX			-
GMFC3 + SCI	XXX	XXX			-
GMFC4 + SCI	XXX	XXX			-
GMFC5 + SCI	XXX	XXX			-
GMFC6 + SCI	XXX	XXX			-

ERG unable to validate discrepancy between these values

Company alternative utility set 1

Company linear regression analysis

- Rescaled all negative values from TTO exercise for EJ states into 0 to -0.594 using linear regression model → removes inconsistencies ERG highlighted

ERG comments

- Company appears to have resolved external validity issue of extreme utilities (most severe rescaled utility is XXX vs -0.389 (worst utility in CLN2 in HST12)
- Negative values rescaled into positive values → LT-/TTO dichotomy of worse-than-death vs better than death has been broken
- Worse than death values in patients without cognitive impairment removed → may not reflect preferences of TTO exercise participants
- Large independent effect of cognitive impairment remains
- Size of decrements in patients with cognitive impairment are large → uncertainty if OTL-200 patients will be spared cognitive decline as motor function declines
- Prefers original ERG value set that preserves worse than death health states in those with preserved cognitive function as rated by public in TTO exercise
- Considers alternative utility set 1 an acceptable compromise if cognitive decrements are to remain, such that most extreme values are brought more in line with UK EQ-5D floor, and other comparable disease areas → scenario on updated ERG base case

Company alternative utility set 2

Company utility 'top-up' for cognitive benefits for OTL-200 patients only

- HRQoL decrement related to loss of cognitive function not captured by loss of motor skills.
  - OTL-200 treated patients in GMFC 3 to 6 show additional benefits beyond GMFC: improved cognitive function, no swallowing/feeding problems, reduction in seizures, bowel and bladder problems, and improvement in vision
- To address ERG's concerns about magnitude of cognitive benefit, company uses normal cognitive utility for each GMFC state and add utility 'top-up' for OTL-200 patients to reflect improved cognitive function and other benefits
- Used utility study in CLN2 to estimate cognitive decrement for patients with severe motor impairment (2-point drop in language equated to a utility decrement of 0.276) → company used 0.276 as a proxy 'top-up' for **80% of OTL-200 treated patients in GMFC 3 to 6**

ERG comments

- **Artificially improves** outlook for patients who stabilise at later stages → significant impact on ICER (**reduce by £153,000 for ES-EJ**)
- Assumes OTL-200 patients have very significant additional benefits
- Company has provided no evidence for additional level of symptom control with OTL-200 → inappropriate to attribute an additive and arbitrary increase in utility for each symptom → any purported resolution of above symptoms may be important as a loss of motor function
- Represents major departure from prior discussions and assumptions underpinning previous utility sets → inappropriate for decision making

⊙ ***How should preserved cognitive function be valued? How were other symptoms (e.g. seizures, pain, feeding, incontinence, sensory function) included in vignettes?***

Company alternative base case

Parameter	Alternative base case	Company comments
Response rate	▪ PS-EJ: XXX full responders ▪ ES-EJ: ○ XXX - GMFC 1 ○ XXX - GMFC 3 ○ XXX - GMFC 4	▪ 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 GMFC 3 or 4
Progression modifier (only changed for ES-EJ)	Set to 1.0 for all values <1.0 Use calculated progression modifier for ES-EJ patients	▪ Clinically implausible that treatment would accelerate disease progression ▪ PS modifiers inappropriate for ES-EJ given different probabilities of stabilisation
Utilities	Rescaled utility (normal cognition) + top-up for OTL-200 patients in GMFC 3 and above	▪ Treatment impacts other symptoms beyond motor function ▪ Approach addresses concerns of utility face validity and level of cognitive decrement
Disease stabilisation	50 years	HSCT only became a viable treatment option 50 years ago
Subgroup distribution		ERG's distribution

ERG revised base case

Parameter	Revised base case
Response rates	▪ Revised based on new data cut ➢ PS-LI: XXX full, XXX stable, XXX unstable ➢ PS-EJ: XXX full, XXX unstable ➢ ES-EJ: XXX unstable
Progression modifier	Progression modifiers used in ES-EJ are equalised with those used in other subgroups
Utilities	ERG's original preferred utility set removing all decrements associated with cognitive impairment. Applied to all groups
Disease stabilisation	20 years
Subgroup distribution	ERG's distribution

Cost-effectiveness results to be discussed in Part 2