NICE National Institute for Health and Care Excellence

For public: All confidential information is redacted ****

Elosulfase alfa for treating mucopolysaccharidosis type 4a [ID1643]

2nd Evaluation meeting – Chair presentation

Chair: Peter Jackson

Lead team: Mark Sheehan, Shehla Mohammed, Lesley Stewart

ERG: BMJ Technology Assessment Group (BMJ TAG)

Technical team: Abi Senthinathan, Christian Griffiths, Jasdeep Hayre

Company: BioMarin

Committee meeting: 13th January 2022

Key abbreviations

CCA	Complete case analysis	NR	Not reported
ESA	Elosulfase alfa	NWC	No wheelchair use
FEV1	Forced expiratory volume in 1 second	OS	Overall survival
FVC	Forced vital capacity	PAS	Patient Access Scheme
HRQoL	Health-related quality of life	QALY	Quality-adjusted life year
ICER	Incremental cost-effectiveness ratio	RDRP	Rare Disease Research Partners
ITT	Intention to treat	SE	Standard error
LY	Life years	SoC	Standard of care
MAA	Managed access agreement	SWC	Sometimes use wheelchair
MAIC	Matched adjusted indirect comparison	WCD	Wheelchair dependent
MPP	Modified per protocol	6MWT	6-minute walk test
MPS IVA	Mucopolysaccharidosis type IVA		

Elosulfase alpha (Vimizim, BioMarin)

Mechanism of action	Elosulfase alfa is an enzyme produced by recombinant DNA technology that provides replacement therapy in conditions caused by N-acetylgalactosamine-6-sulfatase (GALNS) deficiency
Marketing authorisation	The treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages
Dosage and administration	The recommended dose of elosulfase alfa is 2 mg/kg of body weight administered once a week by infusion. The total volume of the infusion should be delivered over approximately 4 hours. This should be supervised by a physician experienced in the management of patients with MPS IVA or other inherited metabolic diseases
Price	• 1x5ml/5mg vial is £750 • Administration cost of £207 • PAS (simple discount) – updated after ECD consultation

Timeline

HST 2: Cost of elosulfase alfa [ESA] (with a patient access scheme) did not reflect value for money for the NHS

Recommended for managed access for 5 year (2015)

MAA agreed with all stakeholders (2015)

ID1643 is re-evaluation of HST 2

MAA twice extended to allow more time for company's submission

Oct 21 (negative ECD)
Jan 22 (ECM 2)

NICE, MPS Society and clinicians worked closely with the company to ensure maximal new data from MAA and further follow up from trials is available for the re-evaluation

Summary of company changes after ECD

- Use alternative baseline characteristics to reflect younger treatment naïve population (data source: MAA treatment naïve and under 6 years old)
- Use ERG preferred bodyweight assumptions
- Use MOR-001 to calculate transition probabilities between baseline to Y1 and Y1 to Y2
- Use alternative utility values
- Discount rate 1.5%
- Updated PAS (not yet approved)

ECD consultation comments

Consultation responses from company, MPS society, Great Ormond Street Hospital (GOSH), RDRP, Birmingham Women's & Children's NHS trust, clinical experts and 11 web comments

Theme	Comments	Notes
Uncaptured benefits	Limited use of the HRQoL collected through the MAA. Uncaptured benefits in clinical practice	Cttee considered uncaptured benefits (see sections 3.7, 3.20, 3.21 in ECD)
Target population	Newly diagnosed populations likely to be younger (< 3 years) and more likely to benefit from treatment. Cost-effectiveness results likely to be better.	Key issue - new ERG scenarios reflecting younger baseline age (but no change to clinical effectiveness)
Long-term benefit & missing data	1. Missing longer term effectiveness data in the model. 2. Need to consider MPS disease registry. 3. Ex-MOR trial patients include long-term data	1. NICE requested long-term data was included in model. Cttee preferred assumptions include very little disease progression for patients having ESA 2. Morquio A Registry Study (MARS) is company held data registry and includes patients from MOR trials. Company included data in original submission to support long-term benefit 3. Company did not provide data for ex-trial patients from start of treatment.

ECD consultation comments

Slide updated after ECM 2

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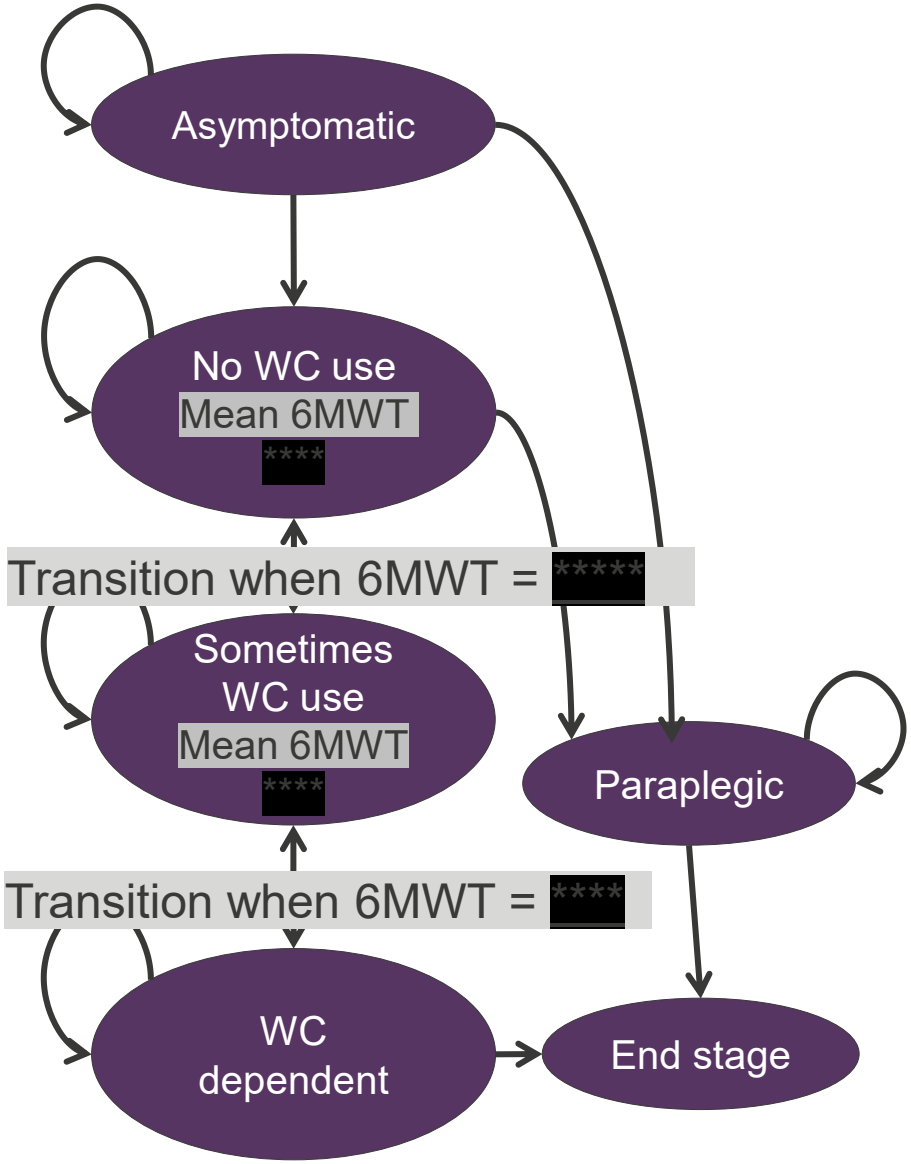
ECD consultation comments

Theme	Comments	Notes
Admin	Non-drug costs should be reduced to account for self-administration	Model includes 90% home administration (50% self/carer, 50% nurse supervised)
Equality	People with disability were excluded from fully contributing to consultation	NICE not informed of issues with documents or asked to make adjustments

Slide updated after ECM 2

Committee preferred assumptions (ECM 1)

ECD	Cttee preferred assumption
Data sources (3.4, 3.6, 3.9)	Both company's and ERG's data sources and complete case analysis (CCA) were acceptable. ERG analysis includes using observed 6MWT & FVC data to estimate mean values for both arms at the end of Y1
Threshold (3.9)	ERG's 6MWT criteria to define movement between health states
Long term benefit (3.10)	• Company's approach for ESA arm is an acceptable proxy for stable disease • ERG's loss of 4.86m for 6MWT in SoC arm is acceptable
Survival (3.11)	OS is linked to lung function
Utility (3.12)	ERG's utility values for SoC arm from the managed access data
Treatment costs (3.13)	Body weight changes over time and reaches 36.7 kg by 18 years



Committee preferred ICERs at ECM1

ERG thresholds	ESA: 1 in 10,000	SoC: 4.86m annual loss	OS linked to FVC	ERG utility (MAA)	ERG's bodyweight	3.5% discount rate
☑	☑	☑	☑	☑	☑	☑

ERG's CCA (scenario 5) includes using observed 6MWT & FVC data to estimate mean values for both arms at the end of Y1

SoC: End of Y1 in model

Health state	End of Y1 6MWT
	Scenario 5
NWC	****
SWC	****
WCD	****

SoC: After Y1 in model

Health state	SoC: Years to progression	
	Scenario 4	Scenario 5
NWC → SWC	****	****
SWC → WCD	****	****
WCD → paraplegic	****	****

Summary of base case assumptions

	Cttee in ECD	Company at ECM 2
Population & analysis	Both company & ERG's CCA plausible: ESA: all MAA or treatment naïve SoC: MOR-001 or MorCAP1	Prefer younger subgroup < 6 years to reflect newly diagnosed population
Entrance & exit criteria	Use ERG's 6MWT criteria to define movement between the health states	☑ ERG correct minor errors
Transition probabilities	ERG CCA used observed 6MWT and FVC data to estimate mean values for both arms at end of Y1	Transition probabilities based on 2 year CCA
Long-term progression	ESA: very little disease progression SoC: 4.86m loss in 6MWT & 0.1L FVC	☑
Overall survival	OS linked to lung function (FVC)	☑
Utility values	Prefer ERG's utility values from MAA & utility gains from ERG's data source (MAA treatment naïve vs. MOR-001)	New utility values for SoC (baseline MAA treatment naïve) & ESA (end of Y2 MAA treatment naïve)
Bodyweight	Body weight changes over time and reaches 36.7 kg by 18 years	Amend baseline age (but use cttee preferred bodyweight)
Discount rate	3.5%	1.5%

ERG – general comments on ECD response

- Company's model changes in response to ECD don't align with company consultation response
- Additional factual accuracy step before ECM 2. Company:
  - Provide rationale for 6 year age cut off for younger MAA subgroup data
  - Report data inconsistency for ex-trial population is corrected but interim data points between the true baseline, clinical trial, and MAA baseline have not been checked and confirmed
  - Provide updated CCA results
  - Use ERG thresholds to define movement in and out of health states
  - Provide raw data to support updated transition probabilities
  - Provide analysis to support updated utility values
  - Provide revised base case ICER
- ERG faced time constraints but validated company's base case after fact check (minor errors corrected). ERG still prefer ERG's 1 year CCA (slide 16) and utility approach (slide 24)

Key Issues

Model driver

Issue	Question for committee
Population & bodyweight	• Is a younger baseline population appropriate to represent treatment naïve patients? • Is the ERG or company approach to age and bodyweight preferred?
CCA analysis & long-term benefit	Is the ERG's scenario analysis for ESA long-term benefit plausible?
Transition probabilities	Is it clinically plausible to assume no patients treated with elosulfase alfa will become wheelchair dependent?
Utility	Are the company's updated utility values acceptable?
Discount rate	Is a discount rate of 3.5% appropriate?

Company's new evidence: Population & weight

ECD

- Cttee noted this review would only focus on people newly diagnosed with MPS 4A.
- Cttee preferred ERG's approach of body weight that changes over time and reaches 36.7 kg by 18 years

Stakeholders

GOSH: GOSH cohort data shows since 2015, median age starting treatment for classical MPS 4A = 3.1years

Newly diagnosed paediatric patients would be expected to be all in the first health state (asymptomatic) at the time of diagnosis

Company

- Prefer baseline characteristics from MAA subgroup < 6 years old (n=[redacted]) to better represent future population who are likely to be younger and benefit more from treatment
  - 6 year age cut off chosen for clinical plausibility (experts suggest newly diagnosed patients around 2-3 years) and analytical purposes (meaningful sample size)
  - Smaller sample but more relevant

Baseline characteristics of MAA population

	<6 years	> 6 years
Age	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]

Baseline characteristics for younger pop

Baseline characteristics by health state for MAA subgroup < 6 years

	Overall	No WC	Some WC	WC dependant
n	[redacted]	[redacted]	[redacted]	[redacted]
Proportion	[redacted]	[redacted]	[redacted]	[redacted]
Age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Company used baseline characteristics from MAA subgroup but amend to accommodate 5% asymptomatic patients

Baseline characteristics for modelled population

Health state	ECM1	ECM2
	Company & ERG	Company
Asymptomatic	[redacted]	[redacted]
No wheelchair use	[redacted]	[redacted]
Sometimes wheelchair use	[redacted]	[redacted]
Wheelchair dependent	[redacted]	[redacted]

ERG: company change baseline age (and proportion starting in each state) but don't amend ERG preferred body weight from ECM 1

Disagree with company's approach as results in clinically implausible combination of patients age and weight. E.g. patients with a mean age of 4 years weigh 19.8kg in NWC but 27kg in SWC. Montaño et al. shows 4 year olds are between 14kg (females) and 15kg (males)

ERG scenario: Population & weight

Cttee's preferred ERG approach to bodyweight assumed patients' weight would increase at a constant rate over the remaining years (from mean age at year 1 until they reached 18 years) and stopped when patients reached 36.7kg

Cttee preferred bodyweight (scenario 4 & 5)

		Baseline		12-month	Increase until 18 yrs	Long-term
Health state	**%**	Age	Weight	Average weight		
Asymptomatic	5%	0	3.6	4.2*	26.04	36.7
No WC use	39%	16	19.8	21.0	15.7	36.7
Some WC use	49%	14	27.0	29.3	7.4	36.7
WC dependent	7%	22	35.2	41.2	-	41.2

ERG scenario at ECM 2 for younger population

	Baseline			Increase until 18 years	Long-term
Health state	%	Age	Weight		
Asymptomatic	5%	0	3.6	26.0	36.7
No WC use	95%	3	13.5	23.2	36.7
Some WC use	0%	-	-	-	-
WC dependent	0%	-	-	-	-

Healthier baseline vs. company approach. GOSH data shows median age for starting treatment with classical MPS 4A is 3.1 yrs. No change in clinical effectiveness for ESA

Is a younger baseline population appropriate to represent treatment naive patients? Is the ERG or company approach to age and bodyweight preferred?

Company's new evidence: CCA & long-term benefit

ECD

Cttee took into account analyses from:

ERG 1 year CCA*	Company 2 year CCA
ESA: MAA treatment naïve subgroup SoC: MOR-001	ESA: MAA SoC: MorCAP1

*use observed 6MWT & FVC data to estimate mean values for both arms at the end of Y1

ERG

ERG's 1 yr CCA has smaller population but is more reliable for assessing changes over time in a clinically heterogeneous population

After factual accuracy check, the company identified and corrected further errors in the MAA ex-trial data. As a result, the ERG's 3 year CCA (ex-trial) to explore long-term impact of ESA on 6MWT is flawed and not presented.

Company

- The ERG's 1 year CCA is too limited so company submit new 2-year CCA with relaxed assumptions of 'CCA per-variable' rather than 'CCA all variables' to maximise the available data while still addressing the missing data issues as much as possible
  - CCA represents a poor approach as it does not manage baseline confounding characteristics such as age or disease severity
  - Linear regression analysis by age band (next slide) confirm long-term benefit across all ages

Company's new evidence: long-term benefit

Linear regression of change in 6MWT in different age groups

Company note improvements/stable disease in all age bands. Based on this, company assume no patients expected to decline to wheelchair dependency if these outcomes were extrapolated over the long-term. Also show younger age group have greater improvement in 6MWT over time

ERG: concerned about robustness of data given small number of patients and limited data collection on lung function in patients aged under 5 years. No consistent trend in efficacy demonstrated

ERG scenario: alternative long-term benefit

ERG

- The ERG remains concerned that the long-term assumption that only 1 in 10,000 ESA patients progresses per year is unsubstantiated
- ERG scenario explores alternative long-term benefit for ESA (based on data from MAA):
  - After Y1 in the model, ESA patients lost *** less than SoC patients in 6MWT, (i.e., *** vs ****m, respectively, annually).
  - Based on pooled results from the MAA and MOR-001, which show that ESA patients had an improvement of **** in their 6MWT compared to SoC patients after year 1.
  - For FVC, the ERG assumed that ESA patients lost ** less than SoC patients, (i.e., ******** vs 0.1L, respectively, annually)

Outcome by health state at baseline	SoC		ESA	
	Company	ERG	Company	ERG
Years taken to change from NWC to SWC	****	14	****	39
Years taken to change from SWC to WCD	****	35	****	77
Years taken to change from WCD to paraplegic	****	7.4	****	7.7

Is the ERG's scenario analysis for ESA long-term benefit plausible?

Company's new evidence: Transition probabilities

ECD

- Cttee considered ERG and company's CCA plausible
- The ERG's approach included using observed 6MWT and FVC data to estimate mean values for both arms at the end of the first year in the model

Company

- The transition probabilities reflect ERG and committee recommendations.
  - For SOC arm the entire MOR-001 data was used (instead of MORCAP1) to calculate transition between different health states from baseline to Y1 and Y1 to Y2

ERG

After factual accuracy check, ERG note company's transition probabilities based on company 2 year CCA while ERG transition probabilities based on 1 year CCA

SoC transitions – baseline to Y1

SoC transition probabilities at ECM 1						
FROM ↓ TO →	No WC use		Some WC use		Always use WC	
	Company	ERG	Company	ERG	Company	ERG
No WC use	****	****	****	****	****	****
Some WC use	****	****	****	****	****	****
Always use WC	****	****	****	****	****	****

SoC transition probabilities at ECM 2						
FROM ↓ TO →	No WC use		Some WC use		Always use WC	
	Company	ERG	Company	ERG	Company	ERG
No WC use	****	****	****	****	****	****
Some WC use	****	****	****	****	****	****
Always use WC	****	****	****	****	****	****

ERG: Company's new analyses show increase in proportion moving from 'some WC use' to 'WC dependent'.

Elosulfase transitions – baseline to Y1

ESA transition probabilities at ECM 1						
FROM ↓ TO →	No WC use		Some WC use		Always use WC	
	Company	ERG	Company	ERG	Company	ERG
No WC use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some WC use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use WC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*sum of the probability of patients transitioning from the NWC state to the SWC [redacted] and to the WCD [redacted] states.

ESA transition probabilities at ECM 2						
FROM ↓ TO →	No WC use		Some WC use		Always use WC	
	Company	ERG	Company	ERG	Company	ERG
No WC use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some WC use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use WC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG: Company's new analyses results in no movement between health states from baseline to Y1 → assumes patients stay in same or similar health state over a lifetime. Company's new analysis assumes no patients are wheelchair dependent at baseline. Because of model structure, no patients treated with ESA move to become wheelchair dependent in modelled time horizon

Markov trace for health state occupancy (ESA)

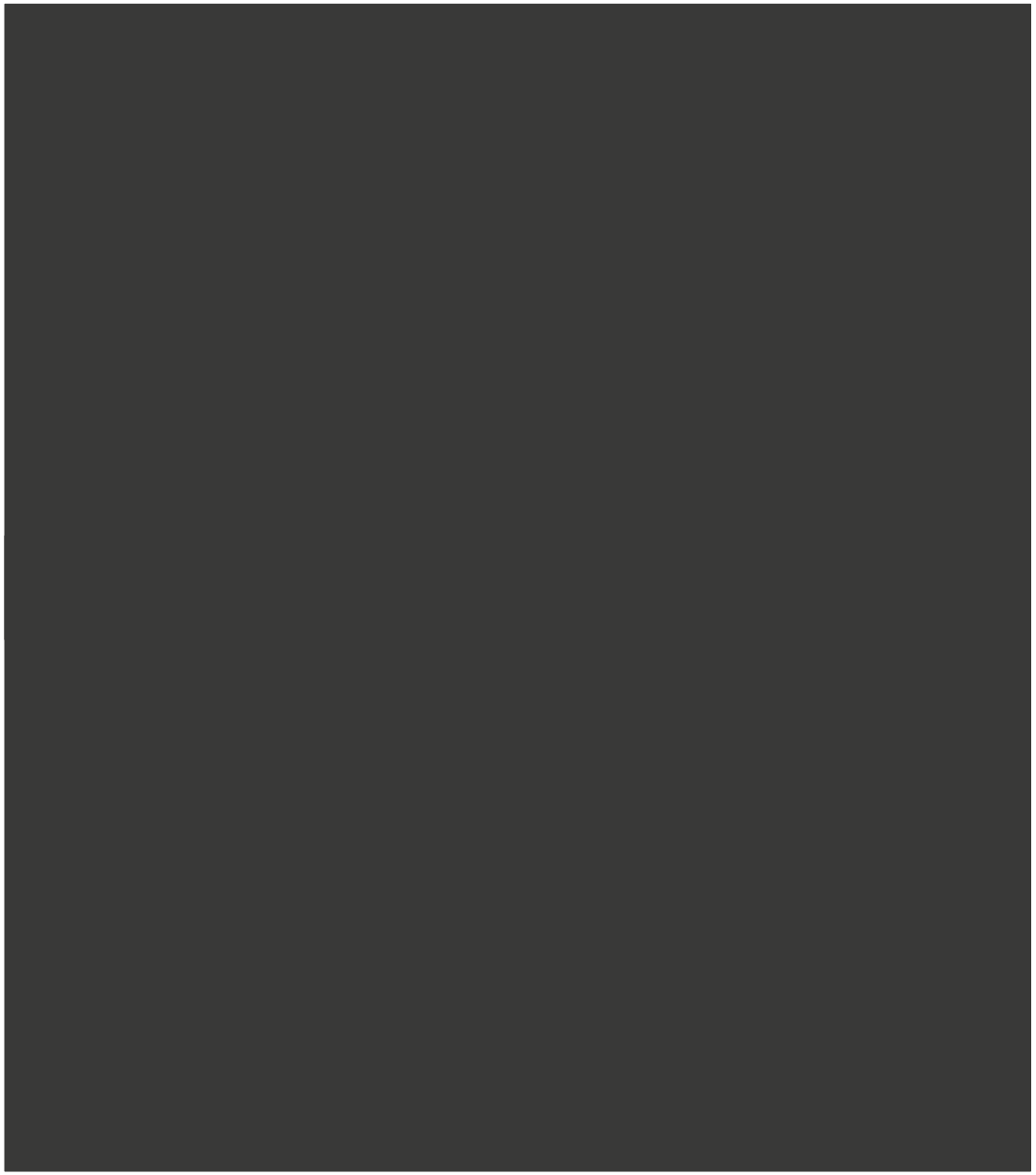
ERG: Company's new analyses (ECD consultation) show better health states for ESA population who are younger at baseline

Key:

- Asymptomatic
- No wheelchair
- Sometimes use wheelchair
- Wheelchair dependent
- Death

Is it clinically plausible to assume no patients treated with ESA will become wheelchair dependent?

ECM 1 – baseline population from MAA



Company's new evidence: Utility values

ECD

Cttee preferred ERG's utility values from the managed access data. These were all baseline values and the same values were used for both treatment arms to avoid double-counting because an additional utility gain is included for elosulfase

Stakeholders

GOSH: little attention has been given to the nuanced and useful qualitative data captured in the HRQL data in the MAA, and has not been taken into account in the model.

Expert: health-related quality of life data completed by parents is likely to have the greatest relevance to this younger target population but this does not appear to have been focussed on in this analysis

MPS society: limited use of the HRQOL collected through the MAA

Company

- Utility values have been updated
  - Accept that utility vales at baseline is appropriate for SoC
  - Prefer utilities at the end of 2 years in the treatment naïve MAA population for elosulfase alfa
- Company also analysed data from the MPS-HAQ questionnaire to understand the broader benefits from treatment and to inform additional utility benefits, which are not captured in the EQ-5D
  - MPS HAQ scores improved in the treatment naïve population over the course of the MAA
  - Correlation analysis showed that EQ-5D is correlated with MPS HAQ, but there may be domains of quality of life not captured well by EQ-5D

Company's new evidence: Utility values

Health state	Standard care				Elosulfase			
	Company ECM 1	Cttee	HST 2	Company ECM 2	Company ECM 1	Cttee	HST 2	Company ECM 2
Asymptomatic	[redacted]	[redacted]	1.00	[redacted]	[redacted]	[redacted]	1.00	[redacted]
NWC	0.578	[redacted]	0.85	0.54	[redacted]	[redacted]	[redacted]	[redacted]
SWC	0.534	[redacted]	0.58	0.41	[redacted]	[redacted]	[redacted]	[redacted]
WCD	0.251	[redacted]	0.06	0.08	[redacted]	[redacted]	[redacted]	[redacted]

*includes utility gain of [redacted] **includes utility gain of [redacted],
¥ includes utility gain of [redacted], † includes utility gain of [redacted]

ERG

- After fact check, the company provided Excel file with utility values.
- ERG found company's revised values were from MAA subgroup aged 6 years and older, treatment naïve and with 2 year CCA for EQ-5D.
- ERG found inconsistencies with company's analysis of data for ESA arm:
  - utility anchored on 2 year values rather than baseline (e.g. 1 patient in [redacted])
- ERG does not consider company approach robust enough to inform ESA arm
- ERG prefer cttee approach (baseline MAA values for SoC and ESA utility gain from linked to changes in FVC and 6MWT). Scenario: HST 2 values (Hendriksz et al. 2014)

Are the company's updated utility values acceptable?

Discount rate

ECD

Cttee noted NICE's interim HST process and methods states that analyses that use a non-reference-case discount rate for costs and outcomes may be considered:

- 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 (usually at least 30 years).

The committee recalled that MPS 4A is progressive and shortens life, and that elosulfase alfa is not curative. It did not consider that elosulfase alfa restored people to full or near full health, so concluded that a 3.5% discount rate was appropriate.

Company

Use 1.5% discount rate:

- MPS IVA is a devastating, progressive and life-threatening disease. Data published by Lavery et al, 2014 highlights the mean age of death as 25.3 years in the UK. Whilst this has improved due to greater disease awareness and management, MPS IVA remains a devastating and life-threatening disease
- Elosulfase has meaningfully modified the disease trajectory, particularly if patients are treated early. It is important to recognise the benefit of initiating treatment as early as possible.
- Long-term data from the MAA supports that elosulfase alfa offers sustained benefits over 10 years.

Company's cost-effectiveness results: ECM 2

ERG thresholds	ERG transitions	ESA: 1 in 10,000	SoC: 4.86m annual loss	OS linked to FVC	ERG utility (MAA)	ERG body weight	3.5% discount
☑	☒	☑	☑	☑	☒	Partially	☒

Company's new analyses at ECM 2 also include:

- amended baseline characteristics to reflect younger population (no patients wheelchair dependent in the elosulfase arm)
- alternative utility values

Company revised base case after factual accuracy check:
1.5% discount rate: ICER **********, undiscounted QALY gain ***** discounted QALY gain *****
3.5% discount rate: ICER **********, undiscounted QALY gain ***** discounted QALY gain *****

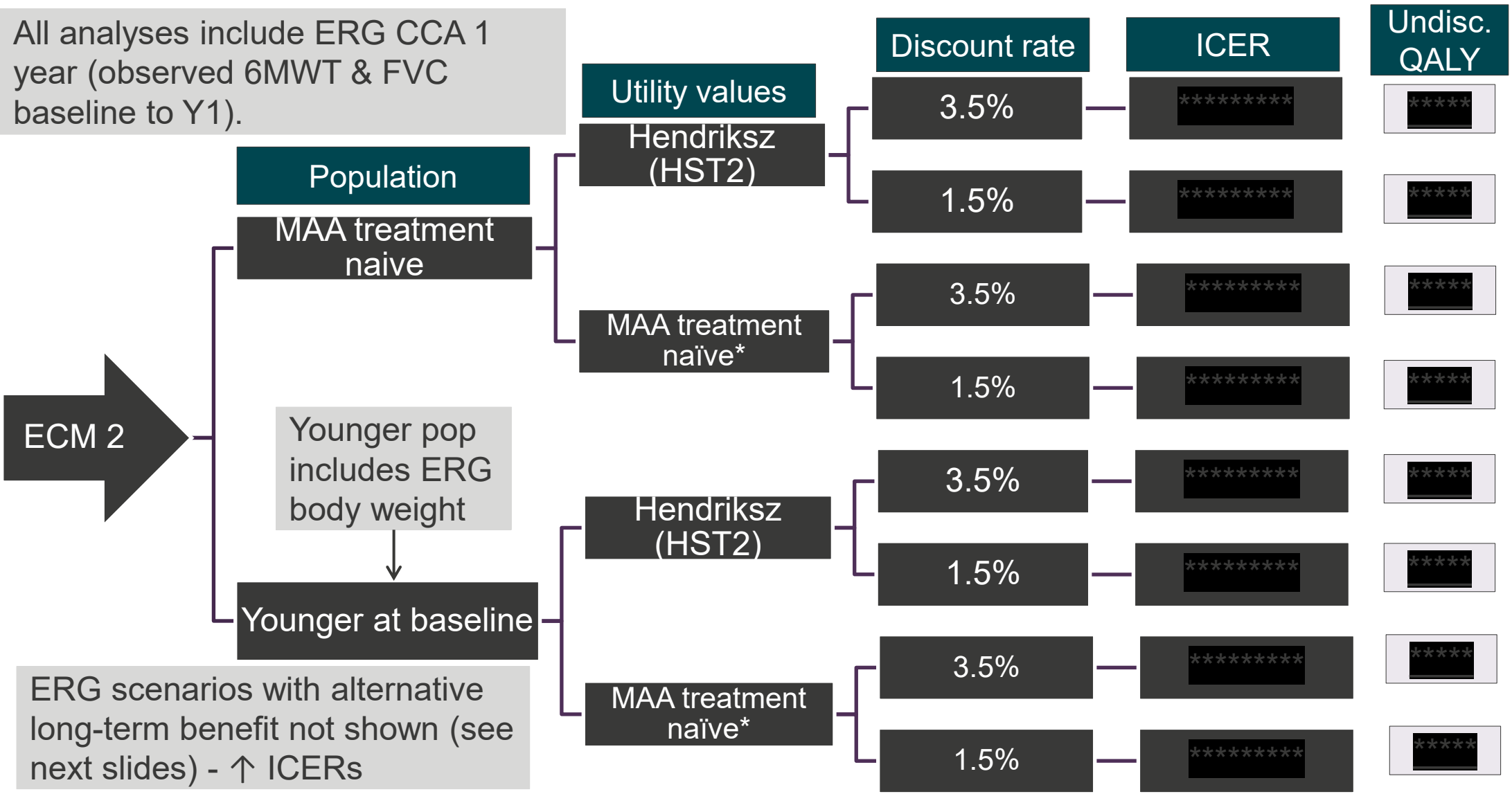
After factual accuracy check, ERG correct minor errors relating to ERG thresholds:
1.5% discount rate: ICER **********,
3.5% discount rate: ICER **********,

NICE

ERG summary ICER tree

ERG thresholds	ERG transitions	ESA: 1 in 10,000	SoC: 4.86m annual loss	OS linked to FVC	ERG utility (MAA)	ERG body weight	3.5% discount
☑	☑	☑	☑	☑	Scenarios	☑	Scenarios

All analyses include ERG CCA 1 year (observed 6MWT & FVC baseline to Y1).



ERG scenarios with alternative long-term benefit not shown (see next slides) - ↑ ICERs

ERG scenarios – MAA treatment naive

Scenario		Incremental			ICER	
		Costs	Disc. QALYs*	Undisc QALYs	3.5%	1.5%
0	ERG corrected company base case	**********	****	****	*********	********
0	Use MAA treatment naive pop	**********	****	****	*********	********
1	Transition probabilities from ERG's 1 yr CCA	**********	****	****	*********	********
2	1 and apply ERG's increase in 6MWT and FVC in the ESA arm from baseline to Y1	**********	****	****	*********	********
3	1 + 2 and utility from Hendriksz for SoC, utility increment for NWC and SWC for ESA	**********	****	****	*********	********
4	1 + 2 and utility from MAA treatment naive for SoC, utility increment for NWC and SWC for ESA	**********	****	****	*********	********
5	1 + 2 + 3 and after Y1 assume ESA patients lose **** and ** less than SoC patients in 6MWT and FVC respectively	**********	****	****	*********	********
6	1 + 2 + 4 and after Y1 assume ESA patients lose **** and ** less than SoC patients in 6MWT and FVC respectively	**********	****	****	*********	********

* Discounted QALYs using 3.5% discount rate

ERG scenarios – Younger population

Scenario		Incremental			ICER	
		Costs	QALYs	Undisc QALYs	3.5%	1.5%
0	ERG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	Use MAA treatment naive pop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	Transition probabilities from ERG's 1 yr CCA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	1 and apply ERG's increase in 6MWT and FVC in the ESA arm from baseline to Y1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	1 + 2 and utility from Hendriksz for SoC, utility increment for NWC and SWC for ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	1 + 2 and utility from MAA treatment naive for SoC, utility increment for NWC and SWC for ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	1 + 2 + 3 and after Y1 assume ESA patients lose [redacted] and [redacted] less than SoC patients in 6MWT and FVC respectively	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	1 + 2 + 4 and after Y1 assume ESA patients lose [redacted] and [redacted] less than SoC patients in 6MWT and FVC respectively	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Discounted QALYs using 3.5% discount rate

QALY weighting

- ICER greater than £100,000 per QALY, judgements take account of the **magnitude of benefit** and the additional **QALY weight** that would be needed to support recommendation
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Number of additional QALYs (X)	Weighting
Less than or equal to 10	1
11 to 29	Between 1 and 3 (equal increments)
Greater or equal to 30	3

Scenario	Incremental QALYs			ICER threshold
	Discounted (1.5%)	Discounted (3.5%)	Undiscounted (0%)	
Company base case	[redacted]	[redacted]	[redacted]	£300,000
ERG (MAA tx naïve)*	[redacted]	[redacted]	[redacted]	Between £100,000 and £300,000
ERG (younger pop)*	[redacted]	[redacted]	[redacted]	
ERG alternative long-term benefit**	[redacted]	[redacted]	[redacted]	

*Excludes ERG scenario with alternative long-term benefit, **Across both populations

Innovation and equality considerations

- Mucopolysaccharidosis type Iva affects children, young people and adults
- HST 2 conclusions
  - Equalities: no specific equalities issues raised
  - Innovation: the committee concluded that elosulfase alfa improved various abilities and aspects of health compromised by the disease, and that the health and quality of life of some patients improved significantly on treatment.
- ID1643 consultation responses relating to equalities:
  - People with disability were excluded from fully contributing to consultation.
  - ECD recommendation is discriminatory → NICE approach shows an unwillingness to use appropriate methodologies for very rare disease.
  - Not appropriate to separate 2 population based on previous treatment. Patients should not be penalised for limitations of early MAA process.

Are there any equality issues to consider in particular, in applying the marketing authorisation of elosulfase alfa and access for people with protected characteristics?

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key Issues

Model driver

Issue	Question for committee
Population & bodyweight	• Is a younger baseline population appropriate to represent treatment naïve patients? • Is the ERG or company approach to age and bodyweight preferred?
CCA analysis & long-term benefit	Is the ERG's scenario analysis for ESA long-term benefit plausible?
Transition probabilities	Is it clinically plausible to assume no patients treated with elosulfase alfa will become wheelchair dependent?
Utility	Are the company's updated utility values acceptable?
Discount rate	Is a discount rate of 3.5% appropriate?

Back up slides

Note: Slide amended after ACM 1

Summary of main clinical evidence

MOR-004 (24 wks) → Part 1 (randomised n=173) → Part 2 (open-label n=169)

MOR-005: Two part open-label extension study for patients from MOR-004

Patients aged 5 years and over from MOR-004 with a 6MWT distance between 30 m and 325 m

- Continue ESA every week or every other week
- Placebo → ESA every week or every other week

→ ESA every week

ERG comments:
- Only licensed dose is **weekly**
- **Prefer data on subgroup who had weekly ESA from start**

MOR-001: Cross-sectional converted to longitudinal

Natural history study of 353 patients → SoC

Post hoc subgroups used to model SoC

- **MorCAP1**: aged 5 yrs and over baseline 6MWT ≥30 and ≤325 m
- **MorCAP 2**: as above but exclude patients having orthopaedic surgery

Company: used MorCAP-1 data for SoC

ERG: don't agree with using MorCAP1 when comparing against MAA because it did not have restriction on 6MWT

Note: Details of MOR-004, 007, 006, 002, 100 not reported here (not used in model)

Summary of MAA data

MAA data (Nov 2019 data cut) Follow up: Dec 2015 to Nov 2019

- **Company**: use full MAA population for ESA arm
- **ERG**: concerned includes ex-trial patients, some not on license dose & uses point of entry to MAA as baseline instead of start of treatment

When using MAA data ERG prefer treatment naïve subgroup

** patients diagnosed with MPS IVA in England

Patients starting ESA for 1st time (ERT-naïve n=**)

Patients previously treated with ESA in MOR trials* (Ex-trial n=**)

Mean treatment duration [redacted] years

Mean treatment duration [redacted] years

ERG: Some patients did not have licensed dose from start – not an issue if use treatment naïve subgroup

*from MOR-002 (n=[redacted]), MOR-006 (n=[redacted]) and MOR-007 (n=[redacted]), MOR-005 (n=[redacted]). Trials had different inclusion/exclusion criteria therefore heterogeneous population

Model inputs at ECM 1

Outcome by health state at baseline	MOR-001		MAA treatment naïve	
	Company model	ERG	Company model	ERG
Mean baseline 6MWT and FVC				
NWC 6MWT	[redacted]	[redacted]	[redacted]	[redacted]
SWC 6MWT	[redacted]	[redacted]	[redacted]	[redacted]
WCD 6MWT	[redacted]	[redacted]	[redacted]	[redacted]
WCD FVC	[redacted]	[redacted]	[redacted]	[redacted]
Mean end of year 1 values using MOR001 and the MAA data				
NWC 6MWT	[redacted]	[redacted]	[redacted]	[redacted]
SWC 6MWT	[redacted]	[redacted]	[redacted]	[redacted]
WCD FVC	[redacted]	[redacted]	[redacted]	[redacted]
Estimates used after year 1 in the model (years to progression to next health state)				
NWC → SWC	[redacted]	[redacted]	[redacted]	[redacted]
SWC → WCD	[redacted]	[redacted]	[redacted]	[redacted]
WCD → paraplegic	[redacted]	[redacted]	[redacted]	[redacted]

*using the alternative 73m exit threshold for the WCD state; ^assuming the same as SoC; $not used in the company's analysis – replaced with assumptions due to lack of clinical plausibility (i.e. use of the 0.01 probability reported in second row of the table)