NICE National Institute for Health and Care Excellence

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

Elosulfase alfa for treating mucopolysaccharidosis type 4a [ID1643]

1st Evaluation meeting – lead team presentation

Chair: Peter Jackson

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Company: BioMarin

Committee meeting: 6 October 2021

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		

Approach to re-evaluation of elosulfase alfa ID1643

2015

- This was the first ever MAA
- An innovative approach for promising new treatments which could not be recommended for use due to significant evidential uncertainty
- The 'review process' following the period of managed access was not described in detail
- If NICE did not recommend elosulfase at the end of the review process, all patients would be required to stop treatment (as outlined in the patient MAA agreements)

2020

- NICE became aware of the stakeholder expectations concerning the re-evaluation
- NICE clarified that the review process would involve a full NICE evaluation with a final recommendation either for routine commissioning or not
- NICE set out exceptional process flexibilities for this re-evaluation, designed to enable patients to continue receiving treatment
- The process flexibilities proposed by NICE recognise the specific circumstances of this re-evaluation – this is not a precedent for other MAAs or commercial agreements

2021

- NHSE and the company will engage in a new round of commercial negotiations, based on the outputs from this re-evaluation of elosulfase
- NICE will make a recommendation concerning continued access for newly diagnosed patients

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

October 2021 **ACM1 TODAY**

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

Drug	Data	
ESA	MOR-005	**Longer term** data available
	MAA	**New** data collected as part of MAA
SoC	MOR-001	No new data

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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 confirmed (simple discount)

Mucopolysaccharidosis type IVa (MPS-IVA)

Mucopolysaccharidosis type IVa (MPS IVA) is an inherited lysosomal storage disorder. It affects males and females equally

MPS IVA is a rare genetic disorder caused by the lack of enzyme needed to break down long carbohydrate molecules. Deficiency leads to progressive tissue damage

Causes wide range of symptoms including joint and skeletal abnormalities (difficulties breathing and moving, spinal instability and spinal cord compression) hearing loss, corneal clouding and heart valve disease

First signs and symptoms typically appear in early childhood. Severe disease causes early mortality. People often need surgery on the neck, hip, knee or leg before 10 years of age

Treatment pathway - No single pathway (symptom relief)

Progressive organ damage → life-threatening complications		Standard care
	Increased cellular accumulation of Glycosaminoglycan (GAG)	No current treatment - bone marrow transplant not successful
	GAG deposition limiting pulmonary function	Steroids, bronchodilators and ventilation
	Cardiac dysfunction due to valve dysfunction	Valve replacement surgery
	Cervical instability and stenosis	Cervical fusion and decompression surgery
	Skeletal dysplasia, hip subluxation etc	Orthopaedic surgery e.g. hip replacement
	Pain in particular arthralgia, limiting mobility	Mild/moderate pain drugs e.g. NSAIDs
	Ear, nose & throst issues e.g. hearing, corneal clouding	Surgery, e.g. ear tube placement
	Frequent surgery risking paraplegia and death	Improved surgical technique

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Patient and carer perspectives

Systematic Experience Reports: RDRP undertook independent research to collect the broader effects of treatment that may be missed by the measures included in the MAA.

Patient experience reports were collected at 4, 8, 12, 24 and 36 months of treatment under the MAA.

Patient/caregiver Survey: Included some patients receiving ESA outside of the MAA

Patient and carer perspectives - submissions from MPS society & RDRP

- Noticeable decline in growth by 18 months (stops by 8 yrs)
- Average height 90 to 150 cm
- Disease becomes more restrictive as child gets older

Symptoms include cervical spine instability; upper airway difficulties, repeated infections, skeletal dysplasia, cardiopulmonary disease (including tracheal stenosis), corneal clouding and hearing loss

A total of 14 broad themes were identified, with 44 subthemes

- Improved endurance was the most common theme overall
- Stability of their condition was more frequently mentioned by prior treated patients

Also report improved mental health (previously missing large periods of school and work)

After treatment with ESA as part of MAA, patients reported improvements in energy, mobility strength and pain. Benefit sustained even for those on treatment for over 10 years

Patient and carer perspectives

Energy
"Never climbed stairs before but now can climb all the way up, able to climb onto the bed, sofa and chairs - couldn't do this before. Energy levels are fantastic. Able to go out on family trips"
(Naïve child – 4 months on treatment)

Mobility
"More content to walk and asking less to be carried. Very noticeable when Father takes him to the shops after school"
(Naïve Child – 8 months)

RDRP - Systematic Collection of Anecdotal Reports

Off treatment (4-5 months, needed port re-sited)
"Vision first thing to be affected. Energy decreased. Not sleeping as well - headaches and nausea on waking morning. Appetite decreased. Emotional wellbeing decreased. More joint soreness, meaning more reliance on painkillers and difficulty moving which restricted their activities.
Now back on Vimizim, energy and stamina increased. Appetite better. Vision improved. General wellbeing improved. Can now move more freely and walk longer again without tiring, meaning they spend more time enjoying life."
(Naïve child – 24 months on treatment)

Pain
"Was seeing a physiotherapist earlier in the year - exercises now feel easy, now exercises without pain. No pain, pain is rare."
(Naïve adult - 12 months)

Well-being
"More get up and go, continued since starting. Psychologically has improved outlook since starting which has continued."
(Naïve adult – 24 months on treatment)

Patient and carer perspectives

"All effects were noticed around 4 weeks after starting. I first noticed that my eyesight improved - notably I could see the legs on a caterpillar which I had never seen before unless in photos. Sight was brighter, sharper, more vibrant.

Due to all the pain and invalidity I was mentally in a very low place, receiving the treatment and reducing my pain, increasing stamina and energy, and my sight, aided in increasing my positivity and my mental health." (Child 11-15)

"I adapt quite quickly, so I can't remember a specific point of feeling any different. But after a few months I noticed that going to concerts, or other activities which would usually leave me tired and in pain for the next few days, was a lot less painful afterward, and for a much shorter time period (like a day). So essentially felt I could do more and not need as much time to recover. (Adult 21-30)

"More subtle in our daughter - not the immediate increase in energy we see with our son. When she started on treatment, she just looked healthier. Was less upset and unsettled, slept better and was happier." (Child 1-5)

MPS Society and RDRP Survey

<u>Changes over time</u>: "These effects continued to improve for a couple of years and have since been maintained. These improvements are now my 'normal' state." (Adult >41)

"Morquio is a progressive disease and without treatment, patients can only deteriorate, not improve. This makes the improvements experienced as a result of Vimizim more significant. It made me realise how much I was putting up with regarding fatigue and pain, because it was all I'd ever known."

Clinician perspectives

Note: Slide amended after ACM 1

BWC MAA experience with 2 cohorts:
- Cohort 1: 4 older patients from trial with ongoing benefit (8-11 years treatment)
- Cohort 2: 8 patients started treatment as part of MAA (7 <5 years and up to 5 years treatment)

Rare disease research partners roundtable discussion with consultants and nurse specialists in Jan 2020

BWC: Cohort 2 not in MOR-005 → improved mobility (respiratory & cardiac testing not relevant due to age)

Clinician perspectives

5 key areas of improvement:
- Improved life expectations
- Fewer respiratory infections
- More energy & resilience
- Better sleep
- More independent

BWC: Cohort 2 families report increased energy in children, particularly in days after their infusion. They remain active and playful and are attending mainstream education where appropriate for their age

Professional statement: Review should focus on gaps in HST2 (real world use and patients excluded from trial)

Based on submissions from Rare disease research partners, Birmingham Women's and Children's NHS Foundation Trust (BWC)

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

[redacted] patients diagnosed with MPS IVA in England

Patients starting ESA for 1st time (ERT-naïve n=[redacted])

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

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

Results from MOR-005 & MAA

- Company report longer-term results from MOR-005 & MAA (see next slides)
- Results are from company's original submission and do not include company's revised analysis using complete case analysis after TE

Endurance (6MWT)

Endurance data suggests some benefit for ESA but data limited

[redacted]

ERG

MAA

- Mean baseline higher in ex-Trial group
- Benefit depends on data used: more improvement using data from the last year with follow-up rather than mean value at last follow-up
- Naive comparison to SoC and based on extrapolation beyond 2 years (simple linear extrapolation may not be appropriate)

MOR-005: Larger benefit using company's preferred MPP pop but ITT results also show sig improvement. Greatest improvement from baseline to week 24 then stable until 2 years. Large decline after but also lower patient numbers. Concerns about number of patients in same data sets from different sources.

Note: Slide amended after ACM 1

Lung function

[redacted]

Difficult to draw conclusions from FVC & FEV1

ERG

MAA

- Mixed results ERT-naïve group show [redacted] but [redacted] with Ex-trial group

MOR-005

- Data for relevant ITT subgroup (continued weekly ESA) suggests ↑FVC from baseline to 72 weeks and 120 weeks.
- Concerns with accuracy of data reporting for FEV1 but [redacted] as FVC

Wheelchair use

WC use assessed subjectively & small patient numbers → data is inconclusive

Wheelchair health state at week 120 (2 years)	Wheelchair health state at baseline					
	MOR-005	MOR-001	MOR-005	MOR-001	MOR-005	MOR-001
	No WC		Occasional WC		Always WC	
No WC	[redacted]					
Occasional WC	[redacted]					
Always WC	[redacted]					

Abbreviations: ESA, elosulfase alfa; QW, weekly; WC, wheelchair.

ERG

MOR-005 baseline to 120 weeks (2 yrs)

Mixed results (open-label by 2 yr)→ possible worsening in 'no WC' group, potential improvement for 'always WC' and no clear benefit for 'occasional WC'.

MOR-005 vs. SoC (MOR-001)

Similar treatment effect at 2 years for 'no WC' and 'occasional WC'. Potential benefit for 'always WC' but based on 1 patient improving in MOR-005 ('always WC' → 'occasional WC')

MAA

Different pattern for 2 subgroups:

- ERT-naïve group: similar change in WC use over time compared with SoC [redacted]
- Ex-trial: [redacted]

At technical engagement ERG had concerns:

- Some MAA ex-trial patients did not have licensed dose of ESA → requested analyses of patients having 'licensed dose' from start of treatment
- Inconsistent timepoints used (e.g. Y1 change from baseline could have been collected up to 3 years after baseline) → requested analyses using 'consistent timepoints'
- Ensure consistent cohort of patients followed up from baseline at each timepoint for each outcome → Requested 'complete case analysis' for each patient & do matching

ERG Issue	Licensed dose		Complete case analysis			Consistent timepoint	
	MOR-05	MAA	MOR-05	MAA	MorCAP-1	MAA	MorCAP-1
Addressed?	☒	☒	☒	☑	☑	☑	☑

Issue	Company after technical engagement
Data consolidation	Study entry = baseline
	Date of assessment used to determine follow-up duration
	Matched timepoints used to compare MAA vs. MOR-001
	Missing values re-coded but no imputation as unlikely to be random & time constraints
Data included?	Complete analyses included data up to **2 years**
New analysis	MAA vs. MorCAP1 only
	No propensity score matching weighting

Complete case analysis (CCA)

Timepoint	Number of complete cases		
	Treatment -naïve	Ex-trial	MAA
Y1	6	2	8
Y2	4	2	6
Y3	0	0	0
Y4	0	0	0

Company investigated number of patients with complete cases across all outcomes. Across the 6 key outcomes in the MAA (6MWT, EQ-5D-5L, FVC, FEV, urinary keratin sulfate, WC status), there were no complete cases after Y2

ERG

- Both ERG and company include patients with data at baseline and subsequent timepoint
  - Outcome based approach rather than requiring all patients to have complete case data for all outcomes
  - Ideally only include patients with data for all outcomes but ERG agree best way to maximise available data
  - But, outcomes likely to be correlated so not ideal to review each outcome independently
  - In both company and ERG approach, each outcome represents different cohort of patients → heterogeneity
- Company's current model structure means clinical data is only used in Y1 of the model
  - ERG limited by company's model structure and use clinical data it considers to be most valid for Y1 model

Company's CCA results

Lung function (FVC, liters)

Timepoint	MAA (****)	SoC (MorCAP-1, ****)
Baseline	******	******
12 months	*******	*******
Mean change from baseline to 12 months	******	******
24 months	******	******
Mean change from baseline to 24 months	*******	*******

Endurance (6MWT, meters)

	SoC (MorCAP-1, ***)	
Health state	Baseline to 12 months	Baseline to 24 months
No WC use	******	******
Some WC use	*******	*******
Always use WC	******	******
Pooled	******	******

Timepoint	MAA ****
Baseline	******
12 months	*******
Mean change from baseline to 12 months	******
24 months	******
Mean change from baseline to 24 months	*******

Company's CCA results

Response (long-term stabilizer or mild decliner)

EQ-5D-5L

Health state	Mean EQ-5D-5L in MAA	n
Pooled	[redacted]	[redacted]
No WC use	[redacted]	[redacted]
Some WC use	[redacted]	[redacted]
Always use WC	[redacted]	[redacted]

Long-term stabiliser: patients whose 24-month 6MWT result was ≥ 6MWT result at baseline

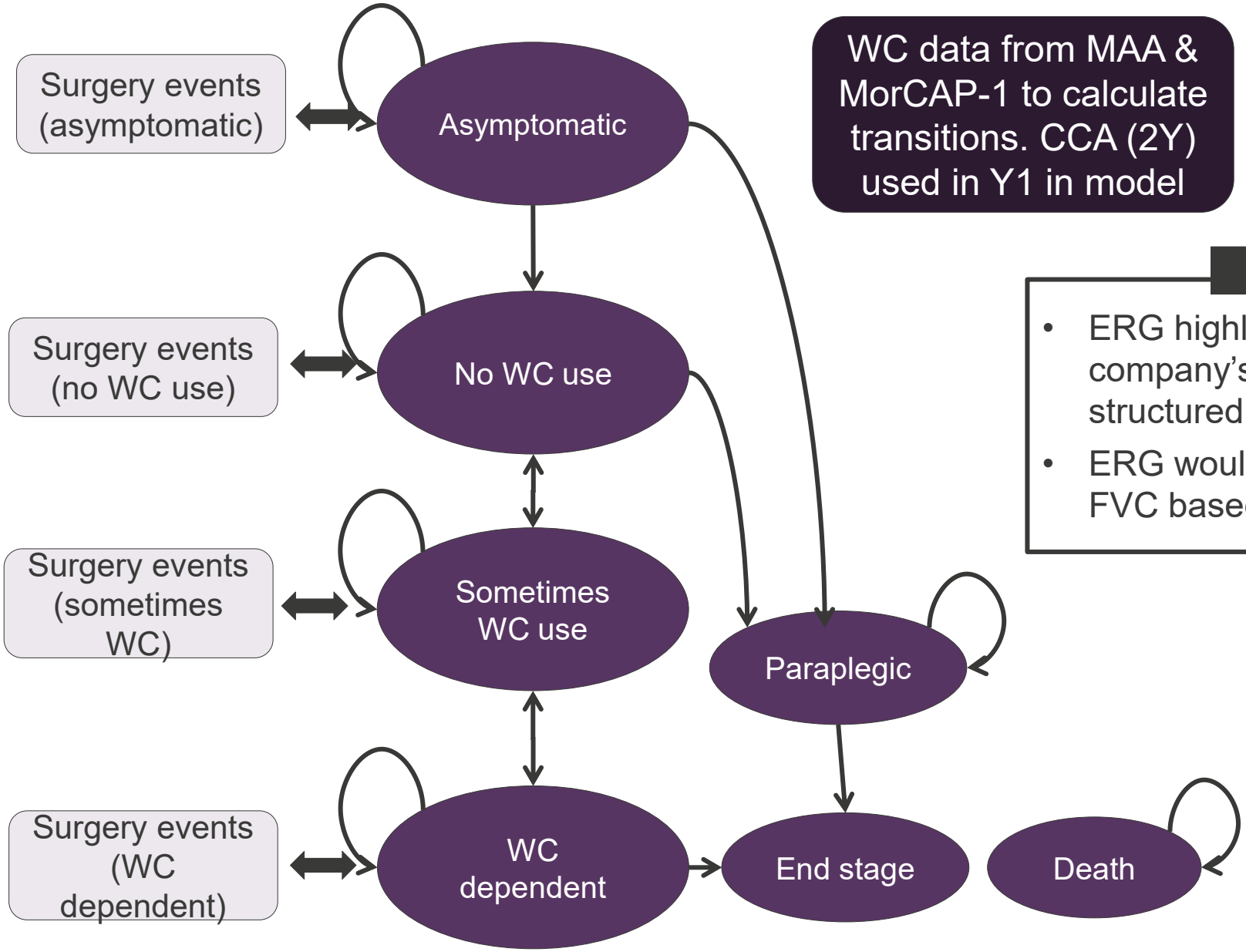
Mild decliner: patients whose 24-month 6MWT result ≤ baseline 6MWT score

HST 2

In HST2 (5.15), the company defined response as:

- 'multi-domain response' if there was any improvement from baseline in endurance (measured using 6MWT or 3MSCT) and any improvement from baseline in pulmonary function
- 'single-domain responders' if there was improvements in either endurance or pulmonary function
- 'non-responders' if they had no improvement in either outcome

Company's economic model



Y1	After Y1
WC data from MAA & MorCAP-1 to calculate transitions. CCA (2Y) used in Y1 in model	Assumptions ESA: very little disease progression SoC: annual loss in 6MWT & FVC

ERG

- ERG highlight limitations with company's model that is structured around WC use
- ERG would prefer 6MWT and FVC based model

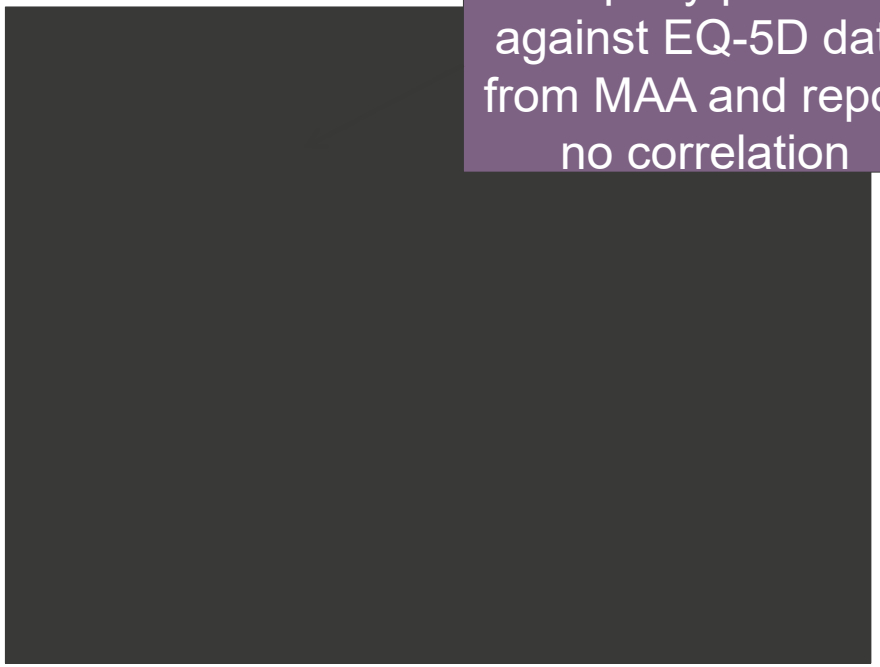
ERG comments on company model

HST 2

HST2 accepted WC model noted:

- 5.2 key determinants of mortality are respiratory & cardiac complications. What matters most is the ability to carry out normal activities with sufficient endurance and without pain or fatigue
- 5.5 patients use WC in different ways to manage endurance and daily activities & do not judge QoL by WC use

Company plot FVC against EQ-5D data from MAA and report no correlation



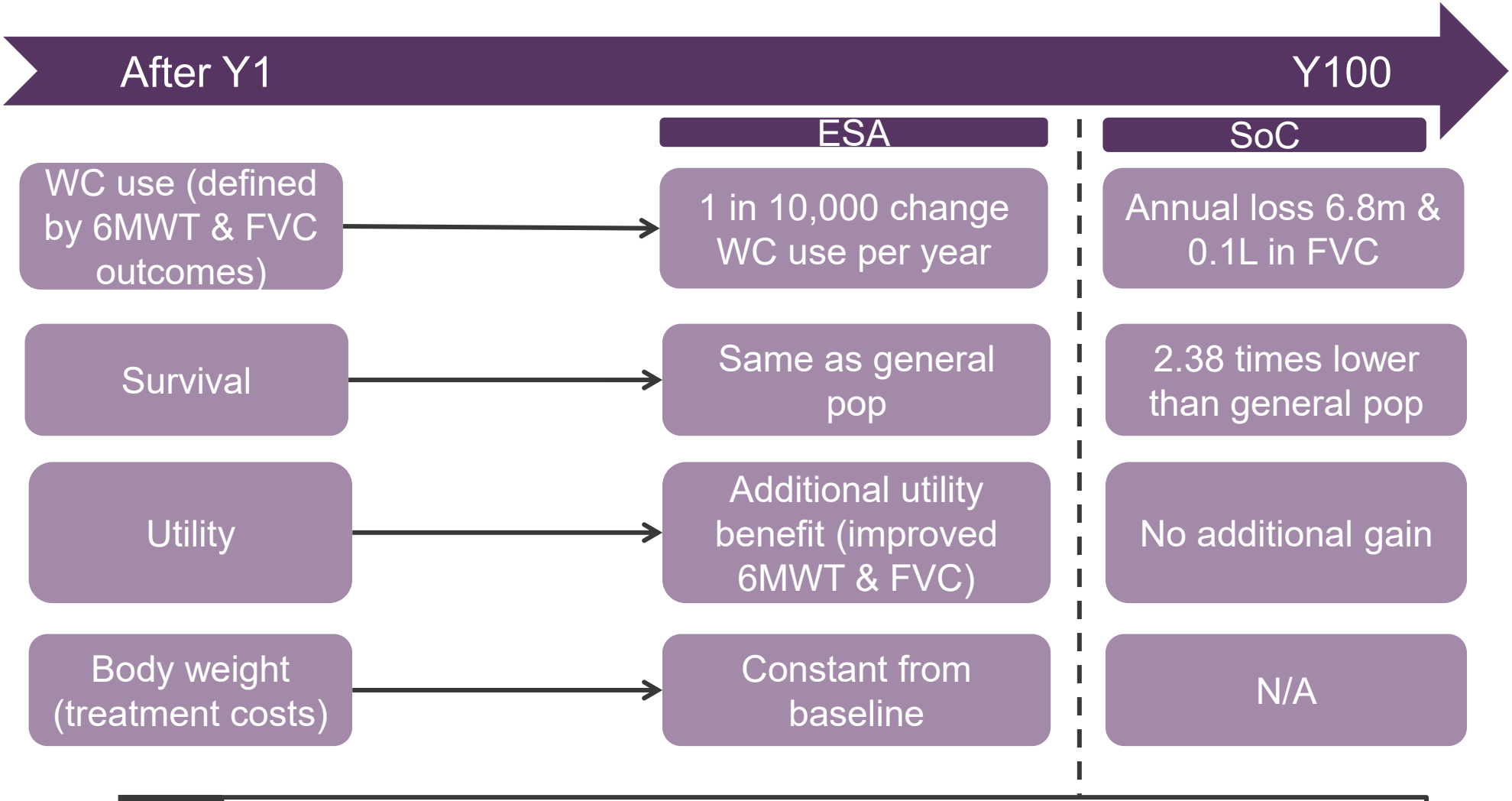
ERG

- MOR-005 found impaired respiratory function is a lead causes of morbidity and mortality
- Company's rationale is inconsistent – suggest weak correlation between EQ-5D & FVC to justify WC based model but strong association to apply utility gain when having ESA
- Model based on respiratory measures could capture disease progression more appropriately

- ERG: company data based on *** patients & included full MAA (including ex-trial population) & 3 different timepoints.
- ERG's analysis shows mean increases in EQ-5D-5L & FVC at every time point → suggest positive trend

Note: Slide amended after ACM 1

Company's model assumptions after Y1



ERG Long-term predictions rely on strong company assumptions – would prefer model that uses more clinical data.

Summary of base case assumptions

	Company	ERG	Cttee (HST2)
ESA arm	All MAA	MAA treatment naïve	MOR-004 & 005
Soc arm	MorCAP1	MOR-001	MOR-001
Data	CCA (Y2)	CCA (Y1)	72-wk from MOR-005
Y1 WC Transitions	Re-estimated using CCA (Y2)	Implausible predictions. Re-estimated using CCA (Y1) data on WC change and redefine the entry and exit thresholds based on baseline MOR-001 data	Based on data from MOR-001 & 005
Benefit after Y1	ESA: Very little progression SoC: annual 6MWT & FVC losses	**From Y1 to Y2**: Relative changes in 6MWT and FVC from CCA (Y1) using MOR-001 and MAA data. **After Y2**: assume ESA and SoC patients have same annual losses in 6MWT and FVC. (Scenario: assuming ESA had an effect every year, both in 6MWT and FVC)	Variable rate of progression across health states
Survival	ESA mortality = general pop	Prefer company scenario: mortality linked FVC decrements. FVC decrements based on the benefit with ESA estimated from the MAA and MOR-001 data	ESA mortality = general pop

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Summary of base case assumptions

	Company	ERG	Cttee (HST2)
Utility values	Use baseline values from MAA treatment naïve. Utility gain for ESA based on assumptions	Company's values do not correspond to baseline utility values. Use values from HST 2. ESA utility gain from MAA treatment naïve	Reasonable to include additional gain but no evidence → not robust
Treatment costs	Assume constant weight from baseline to end of model	Implausible – assume reach 36.7kg by 18 years	Constant weight applied
Discount	1.5% rate applied	1.5% rate applied	Company used 1.5%. ERG suggest could be reasonable

Issues resolved after technical engagement

Issue	Summary	Technical team
1	No direct data to compare ESA vs. SoC	Unresolvable uncertainty - no robust direct comparative data (considered in clinical data issue)
2	Patients in the trials did not all receive the license dose	Not relevant if using treatment naïve subgroup
	Company did not provide analyses using imputations for missing data	Reasonable given heterogeneity of patients
3	No systematic literature review to identify studies for SoC	Company updated an existing systematic review for identifying SoC but approach was very restricted
4	No matched analysis for ESA vs. SoC	Would further reduce sample size but note clinical heterogeneity
5	Inconsistent timepoints	Improvement in data structure – still issues if using full MAA pop
11	Admin & resource use	ERG's updated admin costs & data sources for specialist & palliative care are acceptable
Issues in **blue** are partially resolved		

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Key Issues

Model driver

Issue	Technical team	Question for committee
Clinical data (4 & 6)	• ERG's analysis of MAA treatment naïve vs MOR-001 may be relevant • Concerned by limited use of new data since HST2 • No CCA using MOR-005	What clinical data should be used for decision-making? Are analyses using MOR-005 trial data relevant?
Model structure (7)	Company's WC model may not capture disease progression appropriately	Is the company's WC based model acceptable?
Long-term benefit (8)	Company's assumptions for disease progression after Y1 for ESA may not be clinically plausible	Is it clinically plausible to assume very little disease progression for ESA after Y1?
Survival (9)	Assuming same survival as general pop not realistic & prefer survival linked to FVC	Are the company's survival assumptions plausible? Should survival be linked to respiratory outcomes?
Utility (10)	Prefer utilities from HST 2 & additional gain based on MAA treatment naïve	What data sources should be used to estimate utility values & utility gain for ESA?
Costs (11)	Company may underestimate treatment costs	Is it clinically plausible to assume a constant weight from baseline?
Discount	No company analyses with 3.5% rate	What discount rate should be used?

Clinical data (Issues 4 & 6)

Company

- Data sources
  - ESA: prefer full MAA data
  - SoC: prefer MorCAP-1 (post hoc subgroup of MOR-001)
- In line with ERG request, submitted CCA of MAA and MorCAP-1
  - CCA included patients with data available at Y1 and Y2 (clinical data only used to inform Y1 of the model)

	Issue	ERG comment
6	Data sources	**ESA:** High clinical heterogeneity in full MAA dataset as includes ex-trial patients (not all had licensed dose & company use start of MAA rather than start of treatment as baseline) **SoC**: MorCAP-1 is post hoc subgroup used by company with additional restrictions on inclusion criteria that are not used in MAA
4	CCA	Not appropriate to use Y2 clinical data to inform Y1 of model

→ ERG data sources
ESA: MAA treatment naïve (or MOR-005 but company don't provide updated analyses)
SoC: MOR-001

→ Analyses using 1 year CCA

Company vs. ERG CCA results

Outcome	ESA		SoC	
	Company (CCA Y2 all MAA patients)	ERG (CCA Y1 MAA treatment naïve)	Company (CCA Y2 MorCAP-1)	ERG (CCA Y1 MOR-001)
6MWT (meters)	[redacted]	[redacted]	[redacted]	[redacted]
FVC (Litres)	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L	[redacted]	[redacted]	[redacted]	[redacted]

All results are mean change from baseline pooled across WC states

ERG

- New data was available after HST 2 (up to [redacted] weeks from MOR-005, MAA mean treatment duration [redacted] years ex-trial & [redacted] years treatment naïve) but company CCA limited to MAA 2 years
- Based on provided data & model structure, ERG believe most valid data to use for Y1 model inputs is CCA 1 year
- Company's results from ex-trial and treatment naïve groups in MAA differ

What clinical data should be used for decision-making?
Are analyses using MOR-005 trial data relevant?

Key driver

Company's modelling approach (Issue 7)

Company

- End of year 1 health states occupancy based on WC use data
- Used transition probabilities from CCA (Y2) to estimate transitions from every WC state in both arms of the model from baseline to year 1.
- After year 1, 6MWT and FVC decline assumed from every WC state in the model for SoC patients and no decline (or very little decline) was assumed for ESA patients.

Issue	ERG comment
End of Yr 1 health state	Prefer alternative analyses
Implausible WC transitions	Company's estimated transitions lead to implausible results (↑ in 6MWT with ↑ WC use). Criteria used to define movement in & out of WC states not consistent with clinical data

→ Analyses using WC transition probabilities from CCA (Y1) to predict end of Y1 health state occupancy. From Y1 to Y2 use CCA (Y1), on 6MWT and FVC from MAA and MOR-001. After Y2, assumed same loss in 6MWT and FVC in both arms (alternative scenario: assume same gain used from year 1 to year 2 for every year of the model)

→ Analyses using new thresholds to define entry & exit from WC states

Key driver

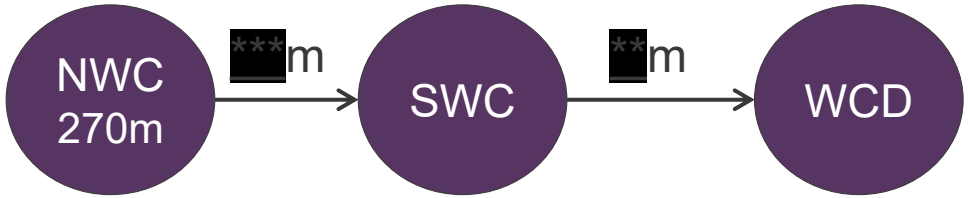
6MWT criteria used to define WC states

Health state	Mean 6MWT	N
No WC use	[redacted]	[redacted]
Some WC use	[redacted]	[redacted]
Always use WC	[redacted]	[redacted]

Company's data from MorCAP-1 shows an implausible increase in mean 6MWT when moving from NWC to SWC

Outcome by health state at baseline	SoC (MOR-001)			ESA (MAA treatment naïve)		
	Mean	SD	n	mean	SD	n
Mean 6MWT at baseline (metres)						
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG's analyses include values with face validity (distance walked in 6MWT ↓ as WC dependency ↑) but note uncertainty for WCD due to small sample size



ERG's 6MWT used to define entry and exit to health states

Is the company's WC based model acceptable for decision-making?

Key driver

WC transitions up to Y1

ESA transition probabilities baseline to Y1 (Company in purple & ERG in black)

FROM ↓ TO →	No WC use	Some WC use	Always use WC
No WC use	*** ***	*** ***	*** ***
Some WC use	*** ***	*** ***	*** ***
Always use WC	*** ***	*** ***	*** ***

*sum of the probability of patients transitioning from the NWC state to the SWC (***) and to the WCD (***) states.

Company assume *** stay in SWC state but MAA data show *** progressed from SWC to WCD

SoC transition probabilities baseline to Y1 (Company in purple & ERG in black)

FROM ↓ TO →	No WC use	Some WC use	Always use WC
No WC use	*** ***	*** ***	*** ***
Some WC use	*** ***	*** ***	*** ***
Always use WC	*** ***	*** ***	*** ***

*company's assumption

Company assume all SoC patients stay in same state but in MOR-001, most patients progressed or improved WC status from baseline Y1

ERG

Distribution of patients at end of Y1 model driver. For Y1 to Y2 prefer use relative changes in 6MWT & FVC. After Y2 same losses in both arms

Key driver

Long term benefit (Issue 8)

HST 2

- Company initially assumed no progression for ESA (multi-domain responders)
- Committee agreed ESA likely to slow progression but not stop it entirely
- Company scenario after consultation: vary rate of progression across health states for multi and single-domain responders (rates based on clinical advice) → explores possibility progression depends on extent of irreversible damage at start of treatment
- Committee concluded assuming no progression for multi-domain responders is not plausible and overestimates benefit. Varying the rate of progression across health states would better reflect natural history of the disease instead of using constant rates

Key driver

Long term benefit (Issue 8)

Issue	ERG comment
Long-term benefit of ESA	No evidence to support assumption of very little disease progression for ESA after Y1
Annual losses for SoC	Lack of robust long-term clinical data
Asymptomatic state	Company assume 3 years for SoC patients to become symptomatic & ESA patients 8 years
Paraplegic and end-stage states	Error in model for probability of cervical fusion in NWC state – ERG not able to correct this

- Scenario: apply ESA treatment effect every year (interpret with caution)
- Analyses applying same losses to both arms
- Scenario: 2 yrs for SoC to become symptomatic & remove ESA delay in onset of symptoms

Key driver

Company's WC transitions for ESA after Y1

WC transitions for patients having ESA and classed 'long-term stabiliser'

	Asymptomatic	NWC	SWC	WCD	Paraplegic	End-stage	Death
Asymptomatic	***	***	***	***	***	***	***
NWC	***	***	***	***	***	***	***
SWC	***	***	***	***	***	***	***
WCD	***	***	***	***	***	***	***
Paraplegic	***	***	***	***	***	***	***
Predeath	***	***	***	***	***	***	***

Assumptions for patients in asymptomatic state:

- SoC: 3 years to become symptomatic (Montano study)
- ESA: Additional 5 years to become symptomatic compared with SoC (clinical advice)

ERG	Scenario: 2 years for patients in SoC arm to become symptomatic & remove delay in becoming symptomatic for ESA arm

Key driver

Other long-term assumptions

Note: Slide amended after ACM 1

	Company	ERG
SoC arm	• Assume patients in NWC and the SWC states lose 6.84m in 6MWT annually (until reach exit thresholds of the WC states). • Assume patients in WCD and paraplegic states lose 0.1L in FVC every year. Once ***L FVC reached they move to the end-of life state	• The 6.84m decrease reported in Harmatz et al. was that of the matched population to the MOR-005 (ITT population: 4.86m) • Company ignore increase in FVC of 2.44% in same population • ERG apply loss of 4.86m from 6MWT & 0.1L FVC annually to both arms after Y2 in the model
Asymptomatic	Probability of progression from asymptomatic to NWC (symptomatic) • 28% for SoC (based on assumption takes 3 years to become symptomatic Montaño et al) • 12% for ESA (based on expert advice take additional 5 yrs vs. SoC)	• Montaño et al – mean age of onset 2 years (ERG scenario: 2 years) • Company assume no progression for ESA in Y1 so 5 year delay is actually 6 year delay (ERG scenario: remove delay)

Is it clinically plausible to assume very little disease progression for ESA after Y1?

Survival (Issue 9)

HST 2

- Company included survival benefit through delaying disease progression & through relative risk of survival. Company assumed same survival as general population for ESA. For SoC survival was 3.03 times lower than ESA
- Committee were uncertain whether company's survival modelling accurately reflected disease related mortality risks (e.g. cervical complications, trauma and heart failure)
- Committee considered scenarios excluding the mortality benefit of ESA to be most plausible (constant mortality across all health states equal to general pop)

Company

- **ESA**: assume survival same as general population (matched age & sex)
- **SoC**: survival is 2.38 times lower than ESA (Quartel 2018)
- **Scenario**: mortality linked to ↓ FVC (not in base case)

Issue	ERG comment
ESA survival	Implausible that survival for ESA patients same as general pop
SoC survival	Company's approach overestimates survival for both treatment arms compared to Quartel et al. 2018
Mortality linked to FVC	Prefer company scenario that links mortality to FVC

Analyses using company scenario mortality linked to FVC:

- Use ERG preferred data & corrections
- Include FVC improvement for ESA
- Apply RR 1.15 for every 10% decrement in FVC

Survival in the model

ERG

- Clinical expert opinion to ERG → clinically implausible to use general pop mortality as ESA does not affect complications of MPS IV (cardiac valvular disease, cervical spinal compromise, chest deformities and tracheal obstruction)
- Mortality for SoC from Quartel (2018) 15-year study of MPV VI patients treated with galsulfase underestimated – should use 15-year KM data
- ERG prefer model that links mortality to FVC decrements

	Quartel	Company
5-year mortality	12.5%	0.03%
Survival at 15 yr	Treated: 65% SoC: 40%	ESA: 99% SoC: 77%

Time in model (years)	Proportion surviving (%)			
	ESA		SoC	
	Company	ERG	Company	ERG
10	**	**	**	**
20	**	**	**	**
30	**	**	**	**
40	**	**	**	**
50	**	**	**	**
60	**	**	**	**
70	**	**	**	**

Note: data extracted by tech team from company's & ERG's post TE models & ERG checked

Are the company's survival assumptions clinically plausible?
Should survival be linked to respiratory outcomes?

Utility (Issue 10)

Company

- SoC & ESA: use MAA treatment naïve baseline
- Utility increment for ESA linked to 6MWT & FVC:
  - 0.02 QALY gain for 10m increase 6MWT
  - 0.2 QALY gain for 1L increase in FVC

HST 2

- Company modelled utility gain for ESA in each health state
- This value was based on improvement in 6MWT & FVC from trials combined with the correlation between 6MWT/FVC and quality of life
- Committee concluded reasonable to include utility gain but, there was lack of evidence so this could not be modelled robustly

Issue	ERG comment
Assume same utility values in both arms	ERG does not consider that the values used by the company correspond to baseline utility values
Utility gain for ESA	Company's methods unclear

→ Analyses using values from HST 2

→ Analyses using MAA treatment naïve vs. MOR-001

Utility values used in model

Health state	Utility values (ID1643)							
	SoC arm			Utility gain		ESA arm		
	Before TE	After TE	ERG	Company	ERG	Before TE	After TE	ERG
Asymptomatic	[redacted]	[redacted]	1.000	[redacted]	-	[redacted]	[redacted]	1.000
No WC	[redacted]	[redacted]	0.846	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some WC	[redacted]	[redacted]	0.582	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WC dependent	[redacted]	[redacted]	0.057	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	0.057	[redacted]	-	[redacted]	[redacted]	[redacted]
End state	[redacted]	[redacted]	0.024	[redacted]	-	[redacted]	[redacted]	0.024

ERG

- Unclear how company estimated utility values for SoC using MAA treatment naïve data – ERG analyses suggest values much lower
  - Reasonable to use utility from HST 2 (Hendriksz)
- Unclear how company estimate data for utility gain
  - Use ERG preferred data sources (MAA treatment naïve vs. MOR-001)

Company suggest weak correlation between EQ-5D & FVC to justify WC based model but strong correlation to apply utility increment for ESA patients

State	Company	ERG
NWC	[redacted]	[redacted]
SWC	[redacted]	[redacted]
AWC	[redacted]	[redacted]

What data sources should be used to estimate utility values and additional utility gain for ESA?

Key driver

Treatment costs (Issue 11)

Background

ESA is an intravenous drug administered weekly over four hours at a dose of 2mg per kilo of body weight

HST 2

Company used average weight in each health state (MOR-001) and assumed remained constant. Patients' weight only changed when transitioning to different health state.

Company

- Treatment costs updated after TE using baseline weight from CCA (2 year) MAA vs. MorCAP-1
- Baseline weight for asymptomatic patients not changed – from MOR-001
- Assume constant weight after baseline

Issue	ERG comment
Baseline weight in WC states	1. For asymptomatic patients, MOR-001 data shouldn't be used 2. For other WC states need to maximise no. patients
Constant weight applied	Company assumes constant weight & underestimates ESA treatment costs

1. Re-estimate mean baseline weight for asymptomatic patients (Montaño 2008).
2. Re-estimated patients' baseline weight in all other WC states, to include max number of patients in the MAA treatment naïve dataset with baseline weight and WC use data.

Analyses assuming on average all patients reach 36.7kg by 18 years

Key driver

Body weight used in model

Company's weight data in model

	Baseline	
Health state	**Age**	**Weight (Kg)**
Asymptomatic	0	****
No WC use	13	****
Some WC use	14	****
WC dependent	17	****

ERG

Re-estimated mean baseline weight for asymptomatic patients based on the Montaño et al (2008):

- Mean weight of males and females with MPS IVA at 0 years is 3.59 kg; and 3.53 kg; respectively.
- ERG weighted these by males (52%) & females (48%) in model → 3.56 kg.

Also re-estimated patients' baseline weight to include maximum number of patients for all other WC states

	Baseline		12-month	Modelled	
Health state	Age	Weight	Weight (estimate)	↑ until 18 yrs	Long-term
Asymptomatic	0	3.6	4.2*	32.5	36.7
No WC use	16	19.8	21.0	15.7	36.7
Some WC use	14	27.0	29.3	7.4	36.7
WC dependent	22	35.2	41.2	-	41.2

Note: all weight data measured in Kg and age in years
* From Montano

ERG try to account for change in weight over time but analyses likely to be conservative (Long-term predictions use mean weight at 18 years)

Is it clinically plausible to assume a constant weight after Y1?

Discount rate

Company

Apply 1.5% discount rate in all analyses in line with HST 2

HST topics

- HST 2 FED states that the company used 1.5% discount rate and the **ERG** considered that this could be reasonable (4.28)
  - In view of other issues and uncertainties and being minded to recommend a MAA, committee did not take a view on discount rate
- Other HST topics of lysosomal disorders have used a 3.5% discount rate
  - HST4 Fabry disease (recommended for people over 16 years of age)
  - HST5 Gaucher disease (recommended for adults)

HST methods

2017 interim HST methods guide states:

- A discount rate of 1.5% for costs and benefits may be considered by the Evaluation 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 Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.

Company's cost-effectiveness analyses

Drugs	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG*	QALYs	Costs (£)	LYG*	QALYs	
Company base case post TE							
SoC	[redacted]	[redacted]					-
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*undiscounted. Costs and QALYs are discounted at 1.5%

ERG cost-effectiveness analyses

Scenario		Incremental		ICER	
		Costs	QALYs	1.5%	3.5%
0	Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Transitions from CCA (Y1) of MAA treatment naïve vs. MOR-001	[redacted]	[redacted]	[redacted]	[redacted]
1+2	• ERG preferred thresholds to define entry and exit to WC states from MOR-001 6MWT • ERG preferred data sources for 6MWT at end of Y1 • Same FVC in both arms at end of Y1 in WCD • After Y1 patients in both arms lose an annual 4.86m in 6MWT & 0.1L FVC.	[redacted]	[redacted]	[redacted]	[redacted]
1 to 4	2 years to become symptomatic (both arms)	[redacted]	[redacted]	[redacted]	[redacted]
1 to 5	Mortality linked to FVC using CCA of MOR-001 & MAA treatment naïve, ESA improved FVC & apply mortality RR 1.15 for every 10% ↓ FVC	[redacted]	[redacted]	[redacted]	[redacted]
1 to 6	Utility values from Hendriksz study for SoC. Utility gain for ESA based on 6MWT data	[redacted]	[redacted]	[redacted]	[redacted]
1 to 8	ERG preferred baseline weights and assume all patients reach 36.7kg by 18 yrs	[redacted]	[redacted]	[redacted]	[redacted]
1 to 9	Updated treatment administration cost	[redacted]	[redacted]	[redacted]	[redacted]

Incremental costs & QALYs are with 1.5% discount rate. ICERs using 3.5% discount rate calculated by tech team

ERG scenarios (cumulative)

Scenario (cumulative ICERs (i.e., adding scenarios 1+2+3+4+5+6+7+8+9, and replacing assumptions where needed)		Incremental		ICER
		Costs	QALYs	
0	ERG's cumulative analysis	[redacted]	[redacted]	[redacted]
a	Using the alternative mean 6MWT distance in the WCD category for all patients in MOR-001 with available 6MWT and WC data at baseline [redacted] (instead of [redacted]).	[redacted]	[redacted]	[redacted]
b	Assuming that SoC patients take longer to progress to the paraplegic state than ESA patients (to reflect the observed data in the MAA and in MOR-001).	[redacted]	[redacted]	[redacted]
c	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state (and assuming no utility increments associated with 6MWT or FVC measures for ESA).	[redacted]	[redacted]	[redacted]
Incremental costs & QALYs & ICERs are with 1.5% discount rate				

ERG scenarios assuming ESA benefit for every year of treatment

Scenario (adding scenarios 1+2+3+4+5+6+7+8+9, and replacing assumptions where needed)		Incremental		ICER
		Costs	QALYs	
0	ERG's cumulative analysis & apply annual ESA benefit	******	****	**********
a	Using the alternative mean 6MWT distance in the WCD category for all patients in MOR-001 with available 6MWT and WC data at baseline **** (instead of ***).	******	****	**********
b	Assuming that SoC patients progress slower than ESA patients to the WCD category (according to the MAA and MOR-001 data).	******	****	**********
c	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state (and assuming no utility increments associated with 6MWT or FVC measures for ESA).	******	****	**********

For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost *** less than SoC patients in their 6MWT, (i.e., *** vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost *** less than SoC patients, (i.e., ******* vs 0.1L, respectively, annually). Incremental costs & QALYs & ICERs are with 1.5% 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	
	Discounted (1.5)	Undiscounted (0%)
Company base case	[redacted]	[redacted]
ERG's analyses	[redacted]	[redacted]

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.

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	Technical team	Question for committee
Clinical data (4 & 6)	• ERG's analysis of MAA treatment naïve vs MOR-001 may be relevant • Concerned by limited use of new data since HST2 • No CCA using MOR-005	What clinical data should be used for decision-making? Are analyses using MOR-005 trial data relevant?
Model structure (7)	Company's WC model may not capture disease progression appropriately	Is the company's WC based model acceptable?
Long-term benefit (8)	Company's assumptions for disease progression after Y1 for ESA may not be clinically plausible	Is it clinically plausible to assume very little disease progression for ESA after Y1?
Survival (9)	Assuming same survival as general pop not realistic & prefer survival linked to FVC	Are the company's survival assumptions plausible? Should survival be linked to respiratory outcomes?
Utility (10)	Prefer utilities from HST 2 & additional gain based on MAA treatment naïve	What data sources should be used to estimate utility values & utility gain for ESA?
Costs (11)	Company may underestimate treatment costs	Is it clinically plausible to assume a constant weight from baseline?
Discount	No company analyses with 3.5% rate	What discount rate should be used?

Back up slides

What is managed access

- An approach to enable patient access to promising new treatments which can not be recommended for routine use due to significant uncertainties in the evidence.
- Further data collection is undertake to assess the clinical benefits of the new treatment
- NICE reviews the new evidence to make a final recommendation about patient access via routine NHS funding
- NHS England and the company have an opportunity for further commercial negotiations with updated information
- NICE may either recommend access for new patients to start treatment OR recommend that no new patients start on treatment if it is not clinically and cost-effective

Benefits of managed access:

- Patients have access to new treatments which NICE would not have recommended
- MAAs are agreed with input from patient groups, clinicians, NHS England, NICE, and the drug manufacturer with input from clinical and patient experts
- Patients receive promising new medicines while further data is collected to strengthen clinical evidence
- Companies have a further opportunity to collect real world data on NHS patients and to make a further submission to NICE to demonstrate the price for their treatment is reasonable based on the clinical benefits patients experience

NICE

ERG cost-effectiveness analyses

Scenario (discounted 1.5% & not cumulative impact)		Incremental		ICER
		Costs	QALYs	
0	Company base case	[redacted]	[redacted]	[redacted]
1	Transitions from CCA of MAA treatment naïve vs. MOR-001	[redacted]	[redacted]	[redacted]
2	• ERG preferred thresholds to define entry and exit to WC states from MOR-001 6MWT • ERG preferred data sources for 6MWT at end of Y1 • Same mean FVC in both arms at end of Y1 in WCD • After Y1 patients in both arms lose an annual 4.86m in 6MWT & SoC patients lose an annual 0.1L FVC.	[redacted]	[redacted]	[redacted]
3	2 years to become symptomatic (SoC arm)	[redacted]	[redacted]	[redacted]
4	2 years to become symptomatic (both arms)	[redacted]	[redacted]	[redacted]
5	Mortality linked to FVC using CCA of MOR-001 & MAA treatment naïve & RR 1.15 for every 10% ↓ FVC	[redacted]	[redacted]	[redacted]
6	Utility values from Hendriksz study for SoC. Utility increments for ESA based on 6MWT data	[redacted]	[redacted]	[redacted]
7	ERG preferred baseline weights	[redacted]	[redacted]	[redacted]
8	ERG preferred baseline weights and MAA Y1 data to estimate ESA costs (all patients reach 36.7kg by 18 yrs)	[redacted]	[redacted]	[redacted]
9	Updated treatments administration cost	[redacted]	[redacted]	[redacted]

ERG scenarios

Scenario (discounted 1.5% & not cumulative impact)		Incremental		ICER
		Costs	QALYs	
0	Company base case	[redacted]	[redacted]	[redacted]
a	Using the alternative mean 6MWT distance in the WCD category for all patients in MOR-001 with available 6MWT and WC data at baseline [redacted] (instead of [redacted]).	[redacted]	[redacted]	[redacted]
b	Assuming that SoC patients take longer to progress to the paraplegic state than ESA patients (to reflect the observed data in the MAA and in MOR-001).	[redacted]	[redacted]	[redacted]
c	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state (and assuming no utility increments associated with 6MWT or FVC measures for ESA).	[redacted]	[redacted]	[redacted]