

**Evidence Review Group Report commissioned by the
NIHR HTA Programme on behalf of NICE**

**Elosulfase alfa for the treatment of mucopolysaccharidosis
type IVA**

ERRATUM

Replacement pages following the factual accuracy check by BioMarin

9th March 2015

Produced by	Southampton Health Technology Assessments Centre
Authors	Keith Cooper, Senior Research Fellow, SHTAC Neelam Kalita, Research Fellow, SHTAC Petra Harris, Research Fellow, SHTAC Andrew Cook, Acting Director SHTAC Jonathan Shepherd, Principal Research Fellow, SHTAC Liz Payne, Research Fellow, SHTAC Emma Loveman, Senior Research Fellow, SHTAC
Correspondence to	Emma Loveman Southampton Health Technology Assessments Centre University of Southampton First Floor, Epsilon House Enterprise Road, Southampton Science park Southampton SO16 7NS

to more severe disease. The transition probabilities between health states are based on the change in wheelchair use (for first cycle only) and decline in 6MWT and FVC (subsequent cycles). Treatment effectiveness is based upon the MOR-005 study for change in wheelchair use and for changes in 6MWT and FVC.

Results are presented for lifetime costs, life years and quality adjusted life years (QALYs) with costs and benefits discounted at 1.5%. After discounting, patients receiving standard care were estimated to have 9.75 QALYs during their lifetime, while patients on elosulfase alfa had 27.83 QALYs, i.e. incremental QALYs of 18.18. The cost for patients over their lifetime was £618,812 for those receiving standard care, compared to [REDACTED] for those receiving elosulfase alfa, i.e. an incremental cost of [REDACTED].

The company's deterministic sensitivity analysis reported both one-way analyses and scenario analyses. These indicated that the model was most sensitive to the discount rate used for costs and QALYs.

The CS concludes that elosulfase alfa brings clear and important clinical benefits resulting in an improvement in survival and QoL and that treatment with elosulfase can be considered cost effective compared with symptomatic standard of care.

Commentary on the robustness of submitted evidence

Strengths

- The assessment of clinical effectiveness is based on a systematic review. There are some minor methodological shortcomings, however, the ERG considers that the evidence identified and included in the submission is generally appropriate to the decision problem and NICE scope.
- The manifestation of the disease appears to vary greatly between patients and this brings challenges to the design of treatment studies. The company have attempted to study this heterogeneous population across a number of studies with reasonable study durations.
- The included studies are of reasonably good quality, in relation to their design. The main issues with the studies are inherent in the design, as the majority are uncontrolled studies, however, they provide the best quality evidence available for the effects of treatment with elosulfase alfa in people with MPS IVA.

Introduction to ERG Report

This report is a critique of the company submission (CS) to NICE from BioMarin on the clinical effectiveness, costs and health effects of elosulfase alfa for mucopolysaccharidosis type IVA. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarifications on some aspects of the CS were requested from the company by the ERG via NICE on (18/12/2014). A response from the company via NICE was received by the ERG on (28/01/2015) and this can be seen in the NICE evaluation report for this evaluation.

BACKGROUND

Critique of the Company's description of underlying health problem

CS section B (CS p. 10 - 12, 33 – 48) provides a clear overview of MPS IVA. However, the overview focuses on more severe manifestations of the condition. Also, spinal complications may be understated. The ERG's clinical advisors comment that cervical instability, hypermobility, acute cord injury and chronic cord compression have a significant impact on neurological outcomes and if severe, have a high risk of mortality. The draft Summary of Product Characteristics (SPC) states that spinal / cervical cord compression was observed both in patients receiving elosulfase alfa and patients receiving placebo in 'clinical trials', but does not refer to specific studies.

Critique of the Company's overview of current service provision

CS section B (CS p. 48 – 54) describes current treatment options. There are no published NICE guidelines or technology appraisals for MPS IVA, but there is a recently published guideline which was funded by the company.¹ While it is accurate to say that management options consist of supportive or palliative care, only drug and surgical interventions are mentioned in the CS. However, the ERG's clinical advisors noted that other interventions, e.g. physiotherapy, chest physiotherapy and occupational therapy¹ are used in practice.

Critique of the Company's definition of decision problem

Population

The population described in the decision problem (CS p. 18 – 19) is 'people with mucopolysaccharidosis type IVA', which matches the NICE scope. This does not differentiate between people with early or later onset disease, or people with a more or less severe condition, or less severe phenotypes of the disease, although the ERG notes this was not part of the NICE scope. For example, some people with MPS IVA may have normal stature, fewer musculoskeletal but more severe cardiac symptoms.¹ Patients with slow-progressing disease can have normal or near-normal life expectancy in contrast with those with rapid progression, as stated in a draft standard operating procedure for the investigation and management of MPS IVA by the Lysosomal Storage Disorders expert advisory group.²

Intervention

The intervention in the decision problem (CS p. 18; p. 20 – 23) is stated as 'elosulfase alfa'. The ERG assumes that this is in addition to established clinical management. Elosulfase alfa has a European marketing authorisation for patients of all ages with MPS IVA, granted in April 2014. Between July 2009 and April 2014, elosulfase alfa had Orphan Drug designation from the European Medicines Agency (EMA: EU/3/09/657). Elosulfase alfa is available in the UK on a compassionate use basis for patients who are in, or have previously participated in clinical studies. In the CS it is stated that 42 patients in the UK (35 in England, CS p. 23) are currently receiving elosulfase alfa on a compassionate use basis. It is not stated what dose of elosulfase alfa is being used in these patients.

Section 8 (CS p. 54 – 59) does not specify the recommended dose of elosulfase alfa. The results of MOR-002 (ascending dose trial) appear to have been used to select the doses for later studies. These were MOR-100 (2.0mg/kg/week), MOR-004 (2.0mg/kg/week vs 2.0mg/kg/two weeks), MOR-005 (2.0mg/kg/week vs 2.0mg/kg/two weeks), and MOR-007 (2.0mg/kg/week). An ongoing study (MOR-008) compares 2.0mg/kg/week vs 4.0mg/kg/week. In Section 8.4 of the CS (p. 55 – 57) it is implied that the duration of treatment is expected to be ongoing unless there are specific clinical reasons to stop. The company's draft SPC states that the recommended dose of elosulfase alfa is 2.0 mg/kg of body weight administered once a week and that the total volume of the infusion should be delivered over approximately 4 hours. The draft SPC also states that the safety and efficacy of elosulfase alfa has not been established in over-65s, so no dosage recommendations are made for these patients. The draft

SPC states that patients should receive antihistamines with or without antipyretics 30 to 60 minutes prior to start of infusion due to the potential for hypersensitivity reactions with elosulfase alfa. None of these details are described in the CS overview.

Comparators

The comparator given in the decision problem (CS p. 18) is 'established clinical management without elosulfase alfa'. This seems appropriate for the NHS and matches the NICE scope. Two of the included studies had placebo comparators (MOR-004 and MOR-005) but all participants had standard clinical management, described by the CS as 'enhanced care' (CS p.137). In general, the ERG considers that the placebo group could be considered as having established clinical management but note that in the MOR-004 trial surgical treatments that may be considered as 'established clinical management' were not permitted (described in more detail below). Some studies presented in the CS were single-arm cohort studies with no comparator.

Outcomes

The outcomes specified by the NICE scope (CS p. 18) are: endurance; mobility; respiratory and cardiac function; growth and development; vision and hearing; sleep apnoea; fatigue; pain; mortality; adverse effects of treatment; and health-related quality of life (HRQoL) for patients and carers. The CS notes that the outcomes used in the included studies vary from these. The CS does not include data on vision and hearing or sleep apnoea (though the CS states that this is evaluated in MOR-006; CS p. 82), but includes data on surgery. The ERG clinical experts comment that sleep apnoea is a significant problem for patients with MPS IVA. The company provided data for these three outcomes in their response to clarification.

All of the reported outcomes appear appropriate and clinically meaningful. The CS also includes surrogate measures for many outcomes and it is unclear how valid and reliable these are for measuring the stated outcomes.

The outcome measures reported in the CS are:

Endurance:

Change in 6-minute walk test (6MWT). This measure has been widely used, but clinically meaningful estimates from other conditions vary,³ and MPS IVA has different characteristics to other conditions. Findings from a chronic heart failure study suggest that the 6MWT may also not be sensitive to change in drug intervention studies, although it is unclear if this applies to disorder such as MPS IVA.⁴ Variations in testing methods that allow for a learning effect or

- oxygen saturation and number of respiratory events per hour were measured during overnight monitoring (Response to clarification questions p. 3).

Hearing:

- Audiometric measurements of hearing ability at various thresholds and frequencies were measured in a small number of participants in MOR-004 (Response to clarification questions p. 2).

Vision

- Presence or absence of corneal clouding was assessed as part of the physical examination in MOR-004 and MOR-005 (Response to clarification questions p. 1).

Mortality:

- Mortality was not measured in the studies in the CS. Mortality risk in the health economic evaluation in the CS is based on assumptions from clinical opinion and studies in patients with MPS VI (CS tables D7, D8, D9, D10).

Composite outcome:

- An analysis of MOR-004 data was carried out with a composite outcome (change in 6MWT, 3MSCT and MVV). The clinical justification for selecting this particular composite measure, and its added value over the individual measures, is not stated in the CS.

Biomarkers:

- While urinary KS was not an outcome listed in the NICE scope, this was presented for the majority of studies and appears to be a relevant surrogate outcome, as urinary KS is a marker of lysosomal cell dysfunction and the aim of elosulfase alfa treatment is to introduce GALNS enzymes into cells to reduce this dysfunction. However, it may be less useful as a patient-centred outcome. Also, KS levels in urine and plasma have been shown to vary with age (with plasma levels peaking between 5 to 10 years of age and urine levels peaking between 1 and 5 years of age) and increase with clinical severity of MPS IVA.⁵

Safety and tolerability:

- Adverse effects include infusion reactions vary from headache, flushing, fever, and/or urticaria to potentially life threatening anaphylactic reactions. Where anticipated, antihistamine prophylaxis was given, as per the draft SPC. The incidence of infusion reactions may increase concomitantly with the increase in dosage.⁶ The draft SPC states that headache, dizziness, breathlessness, diarrhoea, vomiting, oropharyngeal pain, upper abdominal pain, abdominal pain, nausea, chills, and fever were very common in patients treated with elosulfase alfa (frequency $\geq$ 1/10 patients)

Immunogenicity:

- Immunogenic effects are measured in MOR-004 (reported in Qi 2014)⁷, MOR-008 and MOR-100 (both ongoing) (CS Table C7). However, the draft SPC states that all patients developed antibodies to elosulfase alfa in clinical trials and 80% of patients developed neutralising antibodies capable of inhibiting the elosulfase alfa from binding to the cation-independent mannose-6-phosphate receptor. The draft SPC also states that IgE antibodies against elosulfase alfa were detected in $\leq 10\%$ of treated patients, but have not consistently been related to anaphylaxis or other hypersensitivity reactions and/or treatment withdrawal.

Health-related quality of life (patients):

- The impact of MPS IVA on patients' QoL is outlined in terms of daily living activities, loss of endurance and increased wheelchair use, dependency on caregivers, psychosocial, social and emotional impact, and employment (CS Section 7, p. 38 – 40). These outcomes were identified from a natural history study (MOR-001), QoL was formally measured in a QoL (burden of illness) survey (CS p. 39),⁸ from which the CS refers particularly to pain, fatigue, wheelchair and caregiver dependency. QoL was also assessed as a tertiary outcome in MOR-004, using the MPS Health Assessment Questionnaire (MPS HAQ).

Health-related quality of life (carers):

- The impact of MPS IVA on carers' QoL was assessed in a cross-sectional survey (CS Section 7, p. 40 – 43). Caregiver burden was measured with questions derived from the MPS HAQ and the Zarit Burden Interview (ZBI). The MPS HAQ was developed for patients with MPS I and includes daily activities. The ZBI includes five domains: burden in the relationship, emotional wellbeing, social and family life, finances and loss of control over one's life. The amount of time carers spend supporting patients was also assessed.

3. CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company search strategy

The terms selected for the clinical literature search strategy are relevant and comprehensive.

The strategy has some reporting omissions, for example there is no record of the host used for the Embase database, some incorrect syntax and uncertainty in some lines of reporting as to whether all fields had been searched or field limiters had been applied. However, it would appear that nothing of any significance has been lost as a result. On account of the perceived syntax errors, the ERG replicated the Embase search (on Ovid) and obtained different returns

How precise (for example, in terms of confidence interval and p values) are the results?	CS	NR	N/A
	ERG	Unclear	Unclear
Comment: MOR-005 – limited interim results with varying amounts of detail. MOR-007 – interim analysis - limited data reported N/A, not applicable. NR, not reported.			

As can be seen in **Error! Reference source not found.**, there are differences between the CS and ERG quality assessment of MOR-007. Differences were mainly due to the limited amount of detail available.

3.1.5 Description and critique of company's outcome selection

Overall the outcomes included by the company reflect the NICE scope and are appropriate to the decision problem. However, some of the outcome measures employed have issues that need to be fully considered when interpreting results.

6-minute walking test (6WMT)

The 6MWT has been found to vary largely among chronic paediatric conditions by a systematic review published in 2013 based on 15 studies, including 9 different chronic paediatric conditions.¹⁷ In addition, authors investigating the 6MWT in children with sickle cell disease suggest that factors affecting the 6MWT in children and adolescents are not well established.¹⁸ Administration of the test can include variations in the distance between turning points (variation 5–50 metres), lay-out of circuit (circle, squares or use of a treadmill), instructions for turning, as well as differences in encouragements.¹⁹ Standardised administration of the test between different centres is therefore highly important and it is unclear if this was the case in the MOR-004 trial. Information received subsequently from the manufacturer states that the 6MWT was performed according the appropriate guidelines.

3-minute stair climb test (3MSCT)

The metabolic requirements for patients to undertake the 3MSCT depend on factors such as weight, the height of the steps, how fast they are climbed or the amount of support placed on the hand rail.²⁰ Therefore there can be a consequent lack of reference scores to aid clinical interpretation of the test.²⁰ As with the 6MWT, standardised administration of the test between different centres is highly important. The CS states on page 99 that the stairs used for the 3MSCT in MOR-004 were “not standardised and information was not collected regarding individual subject testing conditions (height and girth of stairs as well as availability or quality of handrails, for example, which are critical aids for MPS IVA patients to climb stairs)”.

around 8% of the patients on elosulfase alfa treatment and 18% on placebo had orthopaedic surgery. In response to a clarification request by the ERG, the company reported that in the MOR-004/005 study ■■■ participants underwent surgery (although the ERG notes that the text states ■■■ while the breakdown in clarification response Table 8 shows ■■■). In the QW-QW cohort ■■■ participants underwent surgery. The CS states that there were differences between the ITT and PPP at weeks 48 and 72 due to the exclusion of patients who had orthopaedic surgery and missed multiple doses of study treatment (CS p. 105). In the ITT analysis, patients receiving surgery were reported to have walked zero metres in the 6MWT (CS Table C13.1, p. 90). The patients needing surgery were therefore effectively removed from the analytical group.

Data for the uncontrolled studies are presented descriptively and also graphically over time, to show the change in outcome related to events (for example a change in dosing). Generally, mean changes and SDs are reported and are based on ITT populations. In addition, some z-scores for height/length are presented.

Across the studies in the CS many hypothesis tests have been conducted, but the CS does not explain whether multiplicity is accounted for. The CSR for MOR-004 explains that within each analysis in that trial “the Hochberg method was used for the multiplicity adjustment to maintain the overall Type I error rate of 0.05”, and also that “As an adjustment for multiplicity with the secondary endpoints, a step-down testing procedure was used. The results of the 3MSCT were tested first, and the urine KS results could only be declared significant if the 3MSCT showed a significant result”.

3.1.7 Description and critique of the company’s approach to the evidence synthesis

A narrative review of the various included studies is provided. Results are reported in tables and in text. The narrative reflects the data in the included studies.

As there was only one included relevant RCT, no meta-analysis has been performed.

An indirect comparison was not applicable, as only one relevant RCT was included in the CS.

3.2 Summary statement of company’s approach

The ERG considers that the clinical evidence presented in the CS was not assembled in a fully systematic manner (**Error! Reference source not found.**). The processes for inclusion/exclusion are described (CS p. 61 – 63). However, the evidence base appears to have been narrowed down in a non-systematic process, because the numbers of records in the PRISMA diagram do not appear to follow a logical progression (CS p. 62). Specifically, the number of full-text articles assessed for eligibility

4. Is sufficient detail of the individual studies presented?	Uncertain Summaries of RCTs (MOR-004, MOR-005 and MOR-008) are given (CS tables C5 - C7, p. 68 – 75) and additional information about the numbers of participants analysed in MOR-004 are on CS p. 71. Summaries of non-RCTs are provided (CS tables MOR-001, MOR-002, MOR-006, MOR-007, p. 76 – 83). Differences in study purposes and patient populations in MOR-004, MOR-007, MOR-006 and MOR-008 are outlined (CS p. 84 – 85), but differences in the other studies (MOR-002 and MOR-005) are not described. Information about age-group stratification in the data analysis in MOR-004 is given (CS p. 85 - 86). Consort flow charts are presented for MOR-004, MOR-005 and MOR-009 (CS p. 87 – 88). Only one cohort from the MOR-005 is presented.
5. Are the primary studies summarised appropriately?	Uncertain The results of MOR-004, MOR-005 (interim results), MOR-007 (interim results), MOR-002 and MOR-100 are summarised and presented in narrative form with accompanying charts and tables (CS p. 93 – 119). No results are presented for MOR-006 (results expected [REDACTED]). No results are presented for MOR-008 (results expected [REDACTED]). AE data are presented from MOR-004. The AE results from 6 clinical studies have been combined and summarised in tables and text (CS p. 121 – 125). There is a discrepancy in the numbers of patients in the AE analysis in tables C24 (n=222) and C25 (n=235). The company clarified that n=222 includes all patients from MOR-002, MOR-100, MOR-004, MOR-005, MOR-007 and MOR-008, but it may be that the serious events analysis was carried out at a later date once more patients had been recruited. There is no evidence synthesis of the included studies, but the results of each study are presented qualitatively (CS p. 126 – 134). However, the results of extension studies have been combined with the studies that they have extended (i.e. MOR-004 extension: MOR-005; and MOR-002 extension: MOR-100).

3.3 Summary of submitted evidence

Summary of results for 6-Minute Walk Test (6MWT)

In MOR-004, patients treated with 2.0mg/kg/QW of elosulfase alfa showed a statistically significant increase in distance achieved during the 6MWT at week 24 compared to those treated with placebo (Least Squares (LS) mean difference 22.5; CI 95% 4.0, 40.9; $p=0.0174$). As may be expected in a progressive disease, these gains decline in the extended follow-up offered in study MOR-005 for the ITT population (ITT: LS mean change from baseline 30.1 metres at week 72 compared with 36.5 metres at week 24), although the CS suggests improvements are sustained using the PPP (LS mean change 39.9 metres (CI 95% 26.4, 53.4) from baseline week 24 to 46.0 metres (CI 95% 12.6, 47.6) from baseline week 72). The company provided data for the other cohorts of MOR-005 in their response to the clarification request. On observation of these data the ERG note that at 72 weeks the mean change from baseline for the QoW;QoW treatment cohort in the ITT and PPP were numerically similar to the results from the QW:QW cohort [QoW:QoW: ITT 30.7 (SD 74.92);

MOR-005, QW-QW cohort	2.0mg elosulfase alfa/kg/QW	
Normalised urine KS (% change from MOR-004 baseline, week 72), LS mean difference	ITT: -54.3	-58.3, -50.3; p=N/A
MOR-007 (mean percentage change from baseline) Boys and girls <5 years	2.0mg elosulfase alfa/kg/QW No comparator (n=10)	
Urine KS, (change from baseline, 2 weeks) % (SD)	-43.5 (22.15)	N/A
MOR-002	Elosulfase alfa (see below for doses) (n=20)	
Mean (SD) µg/mg (change from baseline, 24 weeks) ¹	-9 (8)	
Mean (SD) µg/mg (change from baseline, 36 weeks) ²	-13 (9)	
Mean (SD) µg/mg (change from baseline, 72 weeks) ³	-10 (7)	
MOR-100	2.0mg elosulfase alfa/kg/QW (n=17)	
Mean (SD) µg/mg [percent] decrease MOR-002 (baseline, 60 weeks)	-14 (11) [43.7% (26.92)]	
Mean (SD) percent decrease from MOR-002 (baseline, 72 weeks)	35.1% (38.19)	

Source: NR, not reported, N/A, not applicable.

¹ at the end of the 0.1mg/kg/week and 1.0mg/kg/week dose escalation phase; ² at the end of the 2.0mg/kg/week dose phase; ³ at the end of the 1.0mg/kg/week dose reduction phase.

Summary of results for Respiratory function tests

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

MVV

Differences in MVV percentage change from baseline appear to favour the weekly elosulfase alfa treatment (ERG **Table 1**) when compared to placebo in MOR-004 at week 24 (10.3%; CI -1.8, 22.4), as illustrated in CS Figure 12 (p. 96). While this was a tertiary outcome and the trial was not powered to detect changes, the CS suggests nevertheless that there was a trend toward statistical significance (p=0.0943). The ERG notes that this is not statistically significant. The CS presents no long-term data from MOR-005 to support this, instead reporting MVV as part of a composite outcome.

[REDACTED]

[REDACTED]

The CS reports that in the MOR-002 study respiratory function test means were tertiary outcomes. These increased from baseline during the 36-week dose escalation period and continued to increase through the period to 72 weeks. No data are presented for the baseline or interim periods, but data were presented for the 72 week data collection point. The mean percentage increase from baseline in MVV was reported to be 18.4%. The ERG is unable to verify these data.

In MOR-100 at 72 weeks the MVV showed a 10.1% increase from MOR-002 baseline.

Table 1 Changes in MVV

Outcome, follow-up	Intervention/s	95% CI, p value
MOR-004	2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)	
MVV (% change from baseline, week 24), LS mean	PPP 10.3 [REDACTED]	-1.8, 22.4; p=0.0943 (ITT) ² [REDACTED]
MOR-005, QW-QW cohort	2.0mg elosulfase alfa/kg/QW ([REDACTED])	
MVV (% change from MOR-004 baseline, week 72), LS mean ³	[REDACTED]	[REDACTED]
MOR-002	Elosulfase alfa variable doses over 72 weeks (n=20)	
Mean % increase from baseline at 72 weeks	18.4%	
MOR-100	2.0mg elosulfase alfa/kg/QW (n=17)	
Mean (SD) % increase from baseline at 72 weeks	10.1% (27.83)	

¹ Source MOR-005_CSR. ² not powered for statistical comparison.

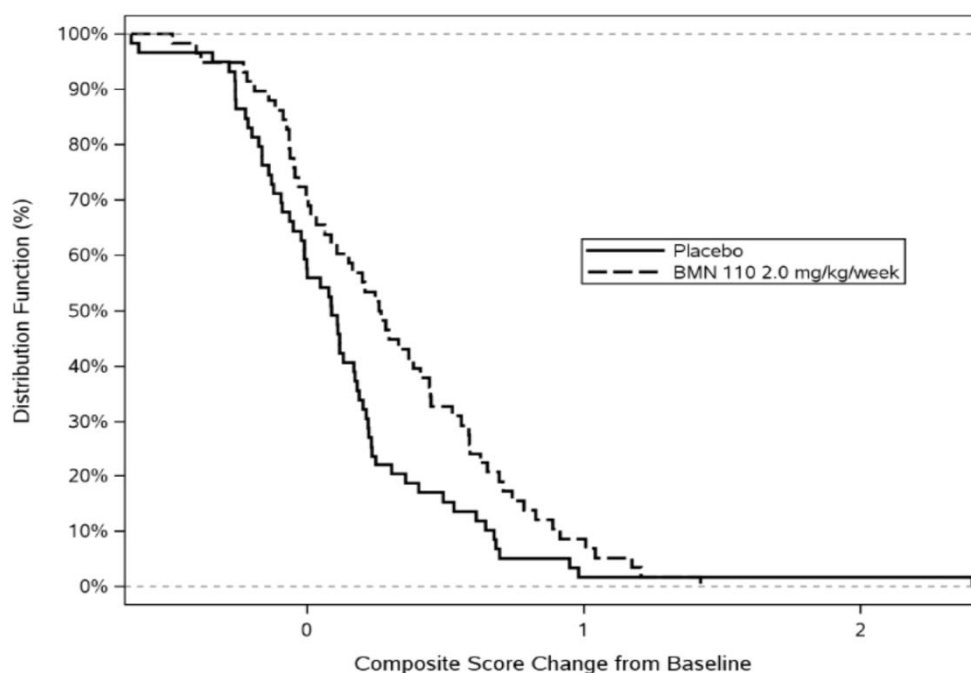
³ Repeated Measures ANCOVA of percent changes from baseline with terms baseline MVV, treatment, time point, interaction of treatment and time point, treatment and time point, age stratification and baseline 6MWT stratification.

PPP, per protocol population. ITT, intention-to-treat analysis. LS, least square. NR, not reported.

FVC

The estimated treatment effect for FVC percentage change from baseline at week 24 in MOR-004 was 3.3% (CI 3.1, 9.6; ITT population) compared with placebo (**Error! Reference source not found.**), favouring the weekly elosulfase alfa treatment. Once again, the trial was not powered to detect changes in secondary outcomes, but the CS reports a statistically non-significant p-value (p=0.3041). The CS suggests that a longer duration of exposure is needed to identify statistically meaningful changes, as it is 'well understood that improvements in pulmonary functions are detectable often after 2 - 3 years of treatment' (CS p. 100). The ERG is not aware of any data to support this statement.

to the placebo group met or exceeded that threshold, although without a statistical comparison, it is unclear if differences are statistically significant.



Source: Hendriksz 2014e.

Figure 1: Responder analysis of 6MWT distance: cumulative distribution for change from baseline to week 24 (ITT). Reproduction of CS Figure 14

In MOR-005 response was assessed in two domains: pulmonary function, as measured by MVV or FVC, and endurance, as measured by 6MWT or 3MSCT for the PPP. An ITT analysis was not conducted There were a total of 56 patients in the MOR-005 QW-QW arm, of which 23 patients were excluded from the PPP who missed treatment doses or who had confounding surgery. All patients in the QW-QW cohort of the PPP (33/33) exhibited a response on either one ([REDACTED]) or both domains ([REDACTED]), the multi-domain responders showing improvements in both pulmonary function and endurance. (**Error! Reference source not found.**). An ITT analysis was not conducted. The remaining [REDACTED] of patients ([REDACTED]) saw an improvement in either pulmonary function or endurance. None of these results are statistically significant, numbers are small, and it is unclear whether these changes are clinically important, therefore results should be viewed with caution. This is particularly the case in the group responding in only one domain: the median patient experiences an [REDACTED] of [REDACTED] in the 6MWT ([REDACTED]) [REDACTED] in FVC (a measure of lung capacity). This seems contrary to the definition of a responder and may be a reporting error, but the ERG does not have the original paired data to investigate further (**Error! Reference source not found.**).

Table 2 Change in weight

Outcome, follow-up	Intervention/s	Treatment effect (95% CI); p value
MOR-007 (change from baseline, week 52) Boys and girls <5 years	2.0mg elosulfase alfa/kg every week (n=10) - No comparator	
Mean change from baseline in kilograms (SD)	1.7 (0.81)	N/A
% change from baseline (SD)	13.8% (7.33)	

N/A, not applicable, SD, standard deviation

Summary of results for wheelchair use

In MOR-004, wheelchair use at baseline was around 13% higher in the placebo group and increased in another 5 patients by week 24, with no increase in wheelchair use in those treated with weekly elosulfase alfa. Results from MOR-005 (CS p. 107) show a change from 'some' wheelchair use at baseline (of MOR-004) to no longer needing it for 2 patients at week 72 (**Table 3**). The CS states that 3 out of 5 patients who were wheelchair-dependent at baseline (always wheelchair use) changed to wheelchair use only sometimes, however the data in Table C20 (p. 107) or Table 1.3.6.3 of the CSR report (p. 56) does not show this (see **Table 3**); it shows no patients as wheelchair dependent at baseline and 2 patients being wheelchair dependent at week 72.

The CS states that ■ of the patients treated with weekly elosulfase alfa in the MOR-005 study reported increased wheelchair use. While the results may be relevant to patients, it must be noted that data are based on a small number of patients.

In addition, the CS presents a table with confidential data (Table C26, p. 128) comparing wheelchair use from untreated patients (27 adults and 36 children aged 7 – 17 years) in the MOR-001 study (week 52) with those in MOR-005 (week 104) to illustrate that elosulfase alfa reduces the degree of progression of the disease and wheelchair dependency, as well as data from a patient-reported outcomes survey (p. 142 – 145) (not presented by the ERG).

Table 3 Wheelchair use

Outcome, follow-up	Intervention/s		p value
MOR-004	2.0mg elosulfase alfa/kg/QW (n=58)	Placebo (n=59)	
No wheelchair use at baseline, n (%)	27 (46.6)	35 (59.3)	
Increase in wheelchair use week 24, n (%)	0 (0)	5 (8.8)	
MOR-005	Baseline (of MOR-004) n (%)		
Wheelchair use week 72 (MOR-005 week 48)	No wheelchair use*	Some wheelchair use*	Always wheelchair use*
No wheelchair	■	■	■

This was based on clinical opinion and evidence in MPS VI patients. The ERG considered this assumption to be optimistic and the ERG clinical experts were unsure about the validity of this assumption. The ERG was also concerned regarding the validity of the assumption that the mortality relative risk of untreated patients was greater than for those treated with elosulfase alfa. The ERG therefore conducted scenario analyses to assess the impact of these assumptions on the base case, details of which are presented in section **Error!** **Reference source not found.**

The ERG is not aware of any existing economic model for this condition. This concurs with the company's statement that the model structure was primarily informed by expert clinical opinion due to lack of existing economic evidence. The ERG considers that patient progression through the disease states was coherently modelled and reflects the underlying biological process.

The ERG considers that the time horizon used in the model is appropriate and encapsulated all the benefits and costs given that the condition is life-long and patients need treatment for the rest of their lives. The cycle length was also considered to be reasonable to examine clinical improvements in the condition. With respect to discount rates, the ERG considers the use of 1.5% discount rate may be reasonable according to NICE recommendations, but a scenario analysis incorporating a rate of 3.5% could have been conducted. The ERG explores this in section **Error! Reference source not found.**

4.2.2 Patient Group

Limited details are given in the CS on the characteristics of the modelled patient population. The CS reports that it is based on the MOR-001 baseline natural history study population, used as a proxy for the prevalent population in the UK (though see below). Patients are assembled into age cohorts based on MOR-001 and proportions in each age cohort were then assigned to a relevant baseline health state (CS Table D1, p. 161 – Note that the paraplegic health state is not included in this table). CS Table D18 reports the average weight for the health states, excluding the paraplegic and end stage health states. The health states have a different starting age (to reflect the initial background mortality rate of patients in that health state) and weight as follows: asymptomatic= 0 years / 12.3kg; non-use of wheelchair= 12 years / 23.3 kg; sometimes use a wheelchair= 17 years / 27.6 kg; always use a wheelchair= 19 years / 27.3kg). The model assumes that patient weight in each health state stays constant. This is unrealistic for children with normal growth and therefore it mainly affects patients in the asymptomatic

The ERG identified computational errors in the estimation of probabilistic values for the following parameters: death, success and paraplegic rates in spinal decompression surgery; FVC improvement in spinal decompression death, success and paraplegic rates; death, success and paraplegic rates in hip surgery; FVC improvement in death, success and paraplegic rates in hip surgery; death, success and paraplegic rates in lower spine surgery; FVC improvement in death, success and paraplegic rates in lower spine surgery; health state costs and annual cost of wheelchair. The ERG corrected these errors and ran the analyses; the results obtained did not differ significantly from the company's results (as shown in Table 32)..

Table 32: Comparison of the PSA results obtained by the company and the corrected results obtained by the ERG

Results obtained by the ERG

PSA results obtained by the company						
	Discounted			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
No Treatment		9.67	27.53		17.35	33.66
Elosulfase Alfa		27.02	61.19			

Corrected PSA results obtained by the ERG

	Discounted			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
No Treatment		9.71	27.75		17.52	33.75
Elosulfase Alfa		27.23	61.50			

There was also an error in the reference cell for mean total life years for elosulfase alfa; the cell was incorrectly referenced to *PSA!AI25* instead of *PSA!AF25* in the model. However, this did not influence the estimation of mean incremental life years.

4.2.10 Comment on validity of results with reference to methodology used

The structure adopted for the economic evaluation reflects the clinical pathway for patients with MPS IVA. However, the ERG has raised a number of concerns regarding the validity of the company's model.

The model makes a number of assumptions from the limited clinical evidence in order to extrapolate results to a lifetime horizon. The model assumes that patients' treatment with elosulfase alfa would lead to a stabilisation of disease for multi-domain responders, i.e. these patients' disease would no longer progress. The ERG considers that this is an optimistic assumption and other plausible scenarios would be more likely, such as treatment causes a reduction in the natural rate of progression.

