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Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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LIST OF ABBREVIATIONS

3MSCT	3 minutes stair climbing test
6MWT	6 minutes walking test
AE	Adverse events
CHMP	Committee for Medicinal Products for Human Use
CS	Company submission
EMA	European Medicine Agency
ERT	Enzyme replacement therapy
ERG	Evidence review group
EPAR	CHMP European Public Assessment Report
ERT	Enzyme Replacement Therapy
FEV_1	1-second forced expiratory volume
FVC	Forced vital capacity
HRQoL	Health-related quality of life
IAR	Infusion associated reaction
ITT	Intent-to-treat
KS	Keratan Sulfate
LS	Lease square
MPS	Mucopolysaccharidosis
MPS HAQ	MPS Health Assessment Questionnaire
MPS IVA	Mucopolysaccharidosis type IVA (also known as Morquio A syndrome)
MPs VI	Mucopolysaccharidosis type VI
MS	Multiple sclerosis
mITT	Modified intention-to-treat
MVV	Maximum Voluntary Ventilation
PBO	Placebo
PODCI	The Pediatric Outcomes Data Collection Instrument
PPP	Per protocol population
PSS	Personal social services
QoL	Quality of life
QW	Weekly
QOW	Every other week
QALY	Quality-adjusted life year
RFT	Respiratory function tests
SAE	Serious adverse events
SCC	Cervical cord compression
SD	Standard deviation
SE	Standard error
SPC	Summary of Product Characteristics
ZBI	Zarit Burden Interview

SUMMARY

Scope of the Company submission

The company's submission (CS) is mostly reflective of the scope of the evaluation issued by NICE. The population is people with mucopolysaccharidosis type IVA (MPS IVA) which matches the scope. The intervention is elosulfase alfa 2.0mg/kg/week in line with marketing authorisation. The comparator is clinical management without elosulfase alfa. The company have presented evidence from one randomised controlled trial (RCT), which had a placebo comparator and is likely to somewhat reflect established clinical management. Other evidence, however, was from uncontrolled studies and caution is recommended in the interpretation of the results of these studies. Outcomes specified in the scope are included in the company decision problem with a few exceptions. These were vision and hearing, and sleep apnoea. However, data for these outcomes were provided as part of the company's clarification responses and have been incorporated into the ERG report.

Summary of submitted clinical effectiveness evidence

The CS presents evidence of the clinical effectiveness of elosulfase alfa based on:

- A three-arm RCT (MOR-004) comparing two different schedules of elosulfase alfa (2.0mg/kg/week; 2.0mg/kg/alternate weeks) with placebo in participants with MPS IVA syndrome (mean age approximately 14 years).
- Interim data from one cohort of an extension study to the MOR-004 trial. The extension study (MOR-005) was a part-randomised study, however, the ERG have considered this as a non-RCT as only one cohort was reported.
- A dose escalation study (MOR-002) with an extension study (MOR-100) in participants aged around 8 years of age.
- Interim data from a single-arm cohort study of children less than 5 years of age (MOR-007).

Two ongoing studies (an RCT, MOR-008; and a single-arm study in those with limited ambulation, MOR-006) were also reported, but these did not contribute any data.

No meta-analyses were conducted.

Quality of the evidence

Overall, the searches conducted by the company were considered by the ERG to be appropriate and likely to have identified all relevant evidence.

The ERG considered that the clinical evidence had not been assembled in a fully systematic way and there were some uncertainties with the quality of the CS based on accepted standards for systematic reviews. These uncertainties were primarily around the validity assessment of the included studies and the level of detail presented for the individual studies.

The quality of the MOR-004 RCT was assessed by the ERG and overall this was reasonable, with some aspects rated as unclear because of lack of reporting. There were a number of uncertainties in the methodological quality of the non-RCTs.

Evidence of the effectiveness of elosulfase alfa

The MOR-004 RCT showed that weekly doses of 2.0mg/kg of elosulfase alfa led to statistically significant improvements in the primary outcome (6-minue walk test; 6MWT) when compared with placebo at 24 weeks. The CS reports that this was a clinically meaningful difference and the ERG clinical advisors concur with this. The ERG note that there is an apparent placebo effect, however, the results still suggest a treatment effect on this surrogate outcome. Other outcomes reported included the 3-minute stair climb test (3MSCT); normalised urine keratan sulfate (KS); the maximum voluntary ventilation (MVV) and other respiratory outcomes; a disease specific measure of quality of life (QoL) and anthropometric measures. None of these secondary or tertiary outcomes were statistically significantly different between treatment groups.

Interim results from the MOR-005 extension study suggest that improvements on the 6MWT and 3MSCT seen in the MOR-004 trial were sustained. However, with no comparator group from MOR-005, the ERG suggests caution in the interpretation of these results. Supporting data presented from the MOR-007 uncontrolled study in a younger paediatric group (aged <5 years) showed gains in objective outcomes such as height and weight measures when compared retrospectively with evidence from a natural history study. A further uncontrolled study, which was an initial dose escalation study followed by a further extension study, showed that in general, outcomes improved from baseline over the 72-week period of study. Results from this study were predominantly to ascertain the licensed dose of elosulfase alfa and

therefore need to be interpreted cautiously. Two other studies have been undertaken by the company, but no results were presented in the CS. Caution is recommended in the interpretation of these results given the uncontrolled nature of these studies.

Adverse events (AEs)

AEs were presented for the MOR-004 trial and for a 'proposed dose population'. The CS does not provide any narrative around the AEs seen in the MOR-004 trial. The ERG note the rate of any AEs in MOR-004 were in the region of 97% in both the treated and the placebo group, although the majority of these were mild or moderate in severity. Drug-related AEs were seen in 61% of the placebo group and 72% of the elosulfase alfa 2.0mg/kg/week group. In the pooled studies data (six studies), approximately 80% reported at least one AE. The most common of those reported were vomiting and pyrexia. The severity of these events was not reported by the CS.

Summary of submitted evidence of costs and health effects

The CS includes:

i) A review of published economic evaluations of treatment of MPS IVA.
ii) A de novo economic evaluation to estimate the costs and health effects of elosulfase alfa compared with current clinical management without elosulfase alfa for people with MPS IVA.

A systematic search of the literature was undertaken by the company to identify previous economic evaluations of treatment of MPS IVA. No relevant studies were identified.

A Markov model was constructed for estimating the costs and health effects of elosulfase alfa compared with current clinical management for people with MPS IVA. The model has six main health states, related to degree of mobility. The starting population is the MOR-001 natural history study population, which is used as proxy for the prevalent population in England. Patients' progression through the model is based upon clinical outcomes of change in 6MWT and respiratory function (based on Forced Vital Capacity, FVC). The model adopted a lifetime horizon, with an annual cycle length and an NHS and personal social services (PSS) perspective.

The economic evaluation makes a number of assumptions, such as patients treated with elosulfase alfa would have a utility benefit, mortality benefit and would be less likely to progress

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 the MOR-004 trial 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 un-controlled studies, however, they provide the best quality evidence available for the effects of treatment with elosulfase alfa in people with MPS IVA.

- The approach taken in the submission to model MPS IVA is reasonable and consistent with the clinical pathway for people with the condition.

Weaknesses and areas of uncertainty

- There is limited randomised study evidence in this area and most of the included studies do not have a comparator. As the natural history of MPS IVA is heterogeneous, it is difficult to establish how robust the estimates of the treatment effect are. The response to treatment appears to vary with wide distributions around the estimates seen and it is difficult to establish if all patients will respond to treatment.
- The one RCT with any data available was of a short duration in the context that treatment will be given for a lifetime. In this trial, only one outcome was statistically significant and it is unclear how effective treatment with elosulfase alfa will be in the long term. In addition, there appears to be a placebo effect in the trial, both on outcomes assessing potential effectiveness and on adverse events.
- The outcomes employed in the included studies are largely surrogate and/or subjective and there are some potential issues with their measurement and their meaningfulness.
- There is likely confounding due to surgery for some patients and while the CS attempts to manage this potential confounding by presenting a per protocol population analysis, the ERG suggest caution in the interpretation of these analyses.
- The CS only includes one study in very young children, which is only partly analysed at the present time. This population may be of more relevance in terms of treatment in the future.
- Adverse events appear to be relatively minor, however, the effects of longer term treatment are unclear.
- The modelled benefits of elosulfase alfa have been overstated and are not consistent with the clinical evidence presented. In particular, there is considerable uncertainty around the long term effect of treatment on disease progression.
- The CS has assumed an additional mortality benefit for elosulfase alfa which appears to double count the mortality effect of the treatment.
- The CS has assumed an additional utility benefit for elosulfase alfa which appears to double count the utility effect of the treatment
- The company model has incorrectly included a reduction in drug costs for patients treated with elosulfase alfa with home infusions due to a VAT waiver.

Summary of additional work undertaken by the ERG

The ERG conducted some additional analyses to investigate a different set of structural assumptions. These were:

- Discount rate of 3.5% for both costs and outcomes
- No reduction in drug cost for VAT for home infusions
- Changes in the assumptions for treatment effect of elosulfase alfa, with respect to:
    - No benefit for single-domain responders
    - Less benefit for multi-domain responders
- No mortality benefit for patients with elosulfase alfa
- No utility increment for patients treated with elosulfase alfa
- Using lower and upper range of 95% confidence intervals for the health state utilities
- Combined scenario of some of the above scenarios

Most of the scenario analyses conducted by the ERG had significant impacts on the model results. The ERG questioned the validity of the company's assumptions for disease progression for multi-domain responders and incremental utilities for patients treated with elosulfase alfa. Scenario analyses with less treatment benefit with regard to disease progression for multi-domain responders resulted in incremental costs of [redacted] and [redacted] for a 50% rate of decline and a natural rate of decline respectively, with associated incremental QALYs of 10.03 and 5.24 respectively. In the scenario with no utility benefit for patients treated with elosulfase alfa, the incremental cost was [redacted] with associated incremental QALYs of 14.22 compared to patients receiving standard of care. Other scenarios including no reduction in drug costs for VAT for home infusion, no benefit in the rate of disease progression for single-domain responders and discount rates of 3.5% for costs and outcomes also influenced the base case results considerably. In addition, a combined scenario also had a significant impact on the model results.

1 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.

2 BACKGROUND

2.1 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 patients with 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.

2.2 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 therapy[1] are used in practice.

2.3 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. The 6MWT may also not be sensitive to change in drug intervention studies.[4] Variations in testing methods that allow for a learning effect or

motivation through verbal cuing may lead to disparate results. Many factors can influence the distance walked: sources of variability in test conduct, training effect, technician experience, subject encouragement, medication, supplemental oxygen, other activities on day of testing, deconditioning and the effect of musculoskeletal conditions.[3] 6MWT multiplied by body weight may be a better measure than 6MWT alone in children.[3] Nevertheless, the ERG's clinical advisors comment that 6MWT has been used in other MPSs, and accepted by the Committee for Human Medicinal Products (CHMP) of the EMA as appropriate outcome measure over 24 weeks.

- Change in 3-minute stair climb test (3MSCT). The ERG is uncertain whether this is an appropriate outcome for the heterogeneous MPS IVA population, many of whom have severe disabilities.

Mobility:

- Wheelchair dependency.

Respiratory and cardiac function

- Respiratory function was measured by FVC, forced expiratory volume in 1 second (FEV_1) and MVV. According to the ERG's clinical experts, these tests are used routinely in clinical practice although not feasible in all patients, for example in those who are wheelchair bound. Cardiac valve function on echocardiogram was an 'exploratory' outcome in MOR-004. That these are tertiary rather than primary outcomes may be surprising given that the CS (p. 37) states that respiratory failure accounts for 63% of patient deaths and cardiac dysfunction accounts for 15% of patient deaths. However, the company use endurance outcomes as a proxy encompassing respiratory and cardiac function.

Growth and development:

- Growth attenuation is one of the main causes of disability in MPS IVA patients, so change in growth and height may be important outcomes in longer-term studies. Likewise, pulmonary outcomes may be considered important primary outcomes in longer-term studies.

Fatigue and pain:

- These outcomes were measured as AEs (CS p. 120). Pain was also assessed in QoL surveys of patients and carers (CS Section 7).

Sleep:

- Presence and severity of sleep apnoea was assessed using a home sleep-testing device in one study. Number of blood oxygen de-saturations ≥3% per hour, minimum blood

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 reason for undertaking this analysis is not stated in the CS and because the analysis is post-hoc, caution is required when evaluating this outcome (see further detail below).

Biomarkers:

- Urinary KS was presented and this appears to be a relevant surrogate outcome, as urinary KS is a marker of lyosomal 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 ≥ 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.

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

on the individual and total line numbers, presumably as a different host was used by the company. The ERG also undertook a Medline search, as this had not been searched separately. Although Medline records are now contained within Embase, the ERG considers it to be best practice to search the originator of the database separately. The ERG searches, however, yielded no extra returns. The Cochrane Library return was similar, although the issue number for the date searched would appear to be incorrect. Centre for Reviews and Dissemination (CRD) databases were checked by the ERG with no extra results found. Overall it does not appear that any relevant studies have been missed.

For ongoing studies the company only reported searching on clinicaltrials.gov. The ERG extended this to include UK Clinical Research Network database, current controlled trials.com, the World Health Organisation International Clinical Trials Registry Platform and EU Clinical Trials Register. The MPS national society website was checked for news of research grants and trials. One additional ongoing study of potential interest was identified by the ERG. This is a single arm, open-label study of elosulfase alfa in an Australian population (ClinicalTrials.gov Identifier: NCT01966029). The study, which is sponsored by BioMarin, started recruitment in July 2013 and will complete by the end of 2015.

The HRQoL search strategy filter contains an acceptable range of general QoL terms, although there is no use of specific paediatric measurement outcome instruments such as PODCI (the Paediatric Outcome Data Collection Instrument). The number of hits returned in line 9 is left blank which lessens transparency. The same errors in syntax reporting occur as in the clinical literature search strategy.

Other further searching undertaken by the ERG included NICE Evidence and the 2014 American Society of Human Genetics conference, with no further useful results being obtained.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The CS clearly states the inclusion/exclusion criteria for published and unpublished studies (p. 61 and 63, respectively) and these are reflective of the decision problem for population and intervention. The population is specified as people with mucopolysaccharidosis, MPS IVA or Morquio A syndrome. The ERG requested clarification over the potential inclusion of other mucopolysaccharidosis conditions and the response received stated that ‘the study selection criteria for population used to select articles from the published literature is focused on

mucopolysaccharidosis IVA. However, the search strategy was expanded to include other mucopolysaccharidosis to ensure that all relevant articles showing the development of long term outcomes of enzyme replacement therapy (ERT) in other MPS diseases were captured'.

Apart from the intervention, no other inclusion criteria were used nor were any exclusion criteria specified. However, on page 67 the CS infers that there was an eligibility criterion on the comparator. No limits were placed on the quality of the included RCTs.

A PRISMA diagram is included on page 62 of the CS, illustrating the number of included and excluded records at each stage. The list of the 64 included references was supplied after a request from the ERG as part of the company's clarification response together with a table showing 14 excluded full text articles. The included number of references in the CS (8) does not reflect the 59 references based on 64 publications shown in the diagram. Clarification received from the company states that 'of the 64 articles deemed relevant (to providing an overview of MPS IVA disease and impact of elosulfase alfa), 'only 3 of the studies provide information on the natural history of the disease and impact of elosulfase alfa on MPS IVA'. Of the excluded full text papers, four are shown as 'full text article not accessible'. While the ERG was only able to access three out of the four papers online, none of the excluded full text articles appear to be trials and therefore of relevance.

The CS does not include a discussion about any potential bias due to the inclusion/exclusion criteria. The only restrictions based on the inclusion/exclusion criteria were the population and intervention, but it is not stated how the inclusion criteria were applied (see below) and it is therefore unclear if there was any bias in study selection.

3.1.3 Identified studies

The CS identified 2 RCTs (MOR-004 and MOR-008) of relevance, of which only one had a comparator of relevance (MOR-004[9]). MOR-004 also had a part randomised extension study (MOR-005[10]), which has been described in the CS as an RCT. However, as previously stated, the ERG has considered the extension study as a non-RCT (see below).

MOR-004 is a phase 3 randomised, double-blind, placebo-controlled, multinational clinical study evaluating the efficacy and safety of 2.0 mg/kg/weekly (QW) and 2.0 mg/kg/every other week (QOW) of elosulfase alfa in patients with MPS IVA, randomising 176 patients ≥5 years of age.

Patients were stratified according to two factors: 6MWT category (≤200 metres and >200 metres) and age group (5 - 11; 12 - 18; ≥19 years) (CS p. 68). Patients had to be able to walk between 30 metres to 325 metres in 6 minutes and were randomised to one of three treatment arms: elosulfase alfa 2.0mg/kg/QW, 2.0mg/kg/QOW or placebo for 24 weeks. Those in the QOW arm were given placebo on the non-treated weeks to mask active drug weeks (details from the trial report). The study was limited to 24 weeks due to ethical concerns related to the exclusion of surgery during the study period. Surgical procedures were denied due to their potentially confounding impact on the results. The study was conducted at 33 study centres in 17 countries worldwide, with 7 study centres located in the UK (n=49: 42 UK-based patients and 7 from overseas). The trial was followed by a 240 week extension study - MOR-005[10] (see 'Non-RCTs' below for more details).

MOR-008 is an ongoing, unpublished, randomised, double-blind, pilot study of the safety and physiological effects of 2 doses of elosulfase alfa in patients with MPS IVA in four countries including the UK. The 27-week phase of the RCT compared 2.0mg/kg/week of elosulfase alfa injections with 4.0 mg/kg/week in 25 patients ≥7 years of age, who can walk at least 200 metres in the 6MWT. Following the study, participants were eligible for entry into an ongoing 130-week extension phase (MOR-100[11] - see non-RCTs). Despite the RCT having no comparator of relevance to the decision problem, the long-term data is of interest to the assessment, as stated on CS page 88 and 134. Enrolment has only just completed and the CS states that only tolerability data are available. Data for sleep apnoea was provided by the company as part of their clarification response.

The CS includes summary details of methodology for both MOR-004 and MOR-008 (p. 68 – 70 and 73 - 75, respectively). Details included location, trial design, study duration, sample size, inclusion/exclusion criteria, method of randomisation (limited detail for MOR-008), method of blinding, intervention/s and comparator/s, statistical methods, and outcomes. The summary tables contain no details of drop-outs / cross-overs, power / sample size calculations or subgroups. Discontinuations are reported in CS Figures 9 and 11 (CS p. 87 - 88) however, and summary details of subgroup analyses from MOR-004 are provided on CS pages 85 - 86. For MOR-004, the CS includes a paragraph explaining the Intention to Treat (ITT)/Per Protocol Population (PPP), stating that the sample size was deemed adequate by the EPAR (European public assessment reports) issued by the CHMP 2014 (CS p. 71). The EPAR also contains details of the sample size calculations (EPAR p.39).

The CS includes flow-charts with the dispositions of patients in the 2 RCTs (CS Figure 9 p. 87 and Figure 11, CS p. 88), including reasons for drop-out where applicable. Baseline characteristics of the population for MOR-004 RCT are located in Appendix 2 (CS p. 247). None were provided for MOR-008, presumably because the data are currently still unpublished.

The company provided electronic copies of MOR-004 including supplements and 2 additional publications[7;12] and following the ERG clarification request the CSR for MOR-004 was submitted. [redacted] Both RCTs were sponsored by BioMarin.

Non-RCTs:

The CS includes a number of published and unpublished non-RCTs (all sponsored by BioMarin), which may have some relevance to the decision problem, but do not include a comparator of relevance to the decision problem:

- MOR-005 (extension to MOR-004; unpublished draft clinical study report (CSR) provided[10] - has a randomised part 1 (MOR-004 completed) and an open-label part 2 (MOR-005 ongoing)
- MOR-002 (BioMarin Data on file – not provided, was an ascending dose trial)
- MOR-100 (ongoing study, unpublished CSR provided[11] and published abstract,[13] is an extension to MOR-002)
- MOR-006 (BioMarin Data on file – not provided, ongoing study)
- MOR-007 (BioMarin Data on file – not provided, published poster provided[14], ongoing study)

In addition, the CS included a published observational study (MOR-001,[15] publication provided), which is a natural history study and not an intervention study. The ERG only focuses on this study in the economic evaluation section of this report (see Section 4).

MOR-005

MOR-005[10] is a 240-week ongoing, unpublished extension study of MOR-004.[9] Part 1 was a randomised, double-blind study that continued until the primary analysis of MOR-004 was complete (30/11/2012), followed by part 2, (initiated 1/12/2012) which is an ongoing open-label study with a single dose regimen of elosulfase alfa (2.0 mg/kg/weekly).[10] In part 1, those in the treated arms in MOR-004 continued with the same treatment, those in the placebo arm were

randomised 1:1 to either treatment dose. There were therefore four cohorts in part 1: QW-QW; QoW:QoW; placebo:QW; placebo:QoW. Those in QOW cohorts were given placebo on the non-treated weeks. In part 2 of MOR-005, all participants transitioned onto 2mg/kg/weekly for the remaining duration of the study. Two participants did not enrol in MOR-005. The cohort sizes were 56, 59, 29, 29 for the four groups respectively. In MOR-005 patients had access to surgery in contrast to MOR-004 where surgery was not permitted, resulting in what the CS describes as a violation of the protocol (Table C13.1, CS p. 90). The CS suggests that this makes the PPP instead of the ITT population more relevant to this evaluation (CS p. 91).

The CS provides a flow chart (CS Figure 10, p.87), methodology summary (p. 71 – 73) and critical appraisal (Table C13.1, p. 90 – 91) for MOR-005, but no baseline characteristics (the company provided some baseline characteristics for MOR-005 as part of their clarification response). [redacted] Results from QW-QW cohort are presented and used in the economic model.

MOR-002 and MOR-100

MOR-002 is a phase 1/2, multi-centre (UK only), open-label, dose-escalation study evaluating the safety, tolerability and efficacy of elosulfase alfa in patients with MPS IVA. This study is based on 20 patients ages 5 – 18 years, receiving elosulfase alfa in an ascending dose: Week 1 - 12: 0.1 mg/kg/week, Week 13 - 24: 1.0 mg/kg/week and Week 25 - 36: 2.0 mg/kg/week. There was an optional continuation of the treatment: 1.0 g/kg/week for 36 - 48 weeks (maximum 84 in total). Patients could enrol in the MOR-100 extension study. In addition, page 138 of the CS states that patients could enrol in the MOR-005 study, but this appears to be a typo and is not stated anywhere else in the CS.

The MOR-100 is an ongoing 240-week extension phase study that includes completed MOR-002 patients and patients from MOR-008 (CS p. 29) - all receiving 2.0mg/kg/week of elosulfase alfa. The CS provides methodology summaries for both MOR-002 and MOR-100 (p. 77 - 78 and p. 78 – 80, respectively, details for MOR-008 as stated above). Baseline characteristics are provided for MOR-002 (Table App4, p. 249 and Table App5, p. 250), but not the extension study MOR-100. A critical appraisal of the study is lacking as the study is reported as ongoing. The study results are of relevance to the assessment of AEs in those treated longer-term with 2mg/kg/week of elosulfase alfa. [redacted]

MOR-006

MOR-006 is an ongoing, unpublished, phase 2, open-label, multinational study evaluating the efficacy and safety of elosulfase alfa in patients with MPS IVA, who have limited ambulation. It is set in 4 countries including the UK. The study is based on 20 planned patients aged ≥ 5 years, who are unable to walk at least 30 metres (p. 133) on the 6MWT and receiving elosulfase alfa 2.0 mg/kg/week for 48 weeks, with an additional 156-week extension phase. Only a methodology summary of the study is provided in the CS (Table C11, p. 80 – 82). The long-term data on outcomes in this more severely affected group would make this study of relevance to the decision problem, however results are not yet available and hence the study will not be considered further by the ERG. [redacted].

MOR-007

MOR-007 is an ongoing, unpublished phase 2, open-label, multinational clinical study evaluating the safety and efficacy of elosulfase alfa in paediatric patients with MPS IVA not eligible for inclusion in MOR-004 (CS p. 67 and 85). The study was undertaken in four countries including the UK. The study included 15 patients age <5 years at the time of 1st administration of the treatment, receiving elosulfase alfa injections at a dose of 2.0 mg/kg/week for 52 weeks, with a 156-week extension phase. The CS provides a critical appraisal (Table C14.2, p. 92), methodology summary (Table C12, p. 82 -83) and baseline characteristics (Table App2, p. 247). The long-term outcome data in this population of younger children make this study of interest to this submission. [redacted].

Baseline characteristics of studies

Table 1 illustrates key baseline characteristics between the three treatment arms in MOR-004. The CS states that demographic characteristics of the included patients were comparable in the three treatment groups at inclusion. The trial publication[9] states that there 'were no meaningful imbalances between treatment groups at baseline in demographic and baseline characteristics' (results section), 'showing a broad distribution of ages, races and ethnicity'. In addition, the CS (p. 89) states that the EPAR reported that there were no obvious imbalances between study groups. The EPAR on page 42 states that there were no relevant differences between groups in demographic baseline characteristics and that baseline disease characteristics were similarly distributed across treatment group. The EPAR also states that:

- 6MWT distance at baseline was higher in the placebo group compared to both elosulfase alfa groups;
- the proportion of patients who used walking aids at baseline was higher in the elosulfase alfa every other week group compared to placebo or elosulfase alfa weekly;
- the number of stairs climbed per minute in the 3MSCT at baseline was lower in the elosulfase alfa every other week group than in the placebo or elosulfase alfa weekly group, while it was comparable between the placebo and the elosulfase alfa/week group;
- that prior medication use of glucocorticoids was higher in the placebo group compared to both elosulfase alfa groups.

The ERG agrees with these observations but agree it does not appear that any of these differences are statistically or clinically meaningful.

Neither the CS nor the trial publication reported a statistical comparison of baseline characteristics between treatment groups. While statistical comparison is not strictly necessary between randomised groups, it does mean that any confounders identified can be accommodated in the outcome analysis.

Table 1 Key baseline characteristics for MOR-004 per treatment arm

MOR-004[1] n (%)	**QW (n=58)**	**QOW (n=59)**	**Placebo (n=59)**
Age, mean (SD), range	13.1 (8.10), 5 - 42	15.3 (10.79), 5 - 49	15.0 (11.30) 5 - 57
Age Group (years),[2] ≥19	10 (17.2%)	12 (20.3%)	14 (23.7%)
Gender, Female Male	32 (55.2%) 26 (44.8%)	25 (42.4%) 34 (57.6%)	32 (54.2%) 27 (45.8%)
6MWT (metres)	203.9 (76.3)	205.7 (81.2)	211.9 (69.9)
Walking aids used	9 (15.5%)	16 (27.1%)	11 (18.6%)
3MSCT (stairs/ minute)	29.6 (16.4)	27.1 (15.8)	30.0 (14.1)

The baselines for MOR-004 reported in the CS have been checked with the trial publication.[9] No baseline characteristics for the population in the MOR-008 trial were provided.
PBO, placebo. QW, weekly. QOW, every other week. [1]Data from Table App1 of the CS (p. 245 - 246).
[2]Stratification factor.

Medication use at baseline per treatment arm was not reported in the CS or the trial publication of MOR-004.

As previously stated, MOR-008 RCT does not have a relevant comparator and therefore does not meet the inclusion criteria of the CS. However, the long-term AE data is of relevance to the decision problem.

Table 2 summarises the patient characteristics of the included non-RCTs, where available, illustrating the differences in the population of these studies. The CS contained no baseline characteristics for MOR-005, but data for 6MWT, 3MSCT, walking aids used during the 6MWT and normalised urine KS were provided as part of company's clarifications responses to the ERG. The company states that imbalances of the MOR 005 placebo switch cohorts were noted in endurance measures and age at week 24/MOR-005 week 0 (placebo group data not shown separately in the ERG report), due to patients receiving placebo in MOR-004 being randomised to elosulfase alfa without stratification for part 1 of MOR-005.

Table 2 Summary of patient characteristics of non-RCTs

Trial name Parameters, mean (SD)	MOR-005[1] QW-QW (n = 56)	MOR-002 (n=20)	MOR-100 (n=17)	MOR-007 (n=15)
Age at Enrolment (years)	NR	[redacted]	[redacted]	3.1 (1.34)
Gender, % Female Male	NR	[redacted]	[redacted]	 53.3 46.7
6-minute Walk Test (metres)	209.4 (71.80)	[redacted]	[redacted]	NR
Used walking aids during 6MWT, n (%)	8 (14.3%)			
Walking Aids Used, %[2] Braces, Afos, Splints Walker None	NR	[redacted]	[redacted]	NR
Wheelchair Use, %[2] No Yes	NR	[redacted]	[redacted]	NR
3MSCT	30.1 (16.24)			
Normalised Urine KS (ug/mg)	27.2 (14.22)			

Data from: Table App2 - MOR-007 (CS p. 247 - 248), App4 and 5 - MOR-002 & 100 (CS p. 249 – 225, Demographics evaluated at the time of enrolment to MOR-002).
NR, Not reported; [1] Data from company's clarification responses. [2] Walking aids and wheelchair use defined per MPS HAQ. Subjects may have used more than one type of walking aid.

3.1.4 Description and critique of the approach to validity assessment

The company assessed the trial quality of MOR-004 but not of MOR-008. Quality assessments for two unpublished non-RCTs [MOR-005 (using RCT criteria) and MOR-007 (using non-RCT criteria)] were also undertaken by the CS. While the CS provided summaries of methodology for

MOR-002 and MOR-100, no quality assessments were provided. As no CSRs are as yet available, the ERG is unable to provide quality assessments for these studies. The company's quality assessment approach for the included RCT was appropriate and based on NICE criteria.

There were some differences between the company's and the ERG assessment of the MOR-004 RCT (see Table 3).

Table 3: Company and ERG assessment of trial quality for MOR-004

1. Was randomisation carried out appropriately?	CS:	Yes
	ERG:	Yes
Comment: randomisation ratio was 1:1:1 and stratified. The CS states that the randomisation schedule was developed by an independent third party (CS p. 69), but details of the procedure were not reported. However, details provided in the clarification response suggest this was appropriate.		
2. Was concealment of treatment allocation adequate?	CS:	Yes
	ERG:	Yes
Comment: details about the concealment of treatment allocation were not reported in the original CS. Clarification received from the company states that allocation to the treatment sequence was concealed as per protocol, although no details about the procedure were provided. As part of the clarification request the CSR for MOR-004 was submitted and the ERG confirm that this states (p. 80) [redacted]		
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes
	ERG:	Unclear
Comment: it is unclear if differences in 6MWT, 3MSCT and walking aid use between the treatment groups at baseline are clinically meaningful.		
4. Were care providers, patients and outcome assessors blind to treatment allocation?	CS:	Yes
	ERG:	Yes
Comment:		
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No
	ERG:	No
Comment:		
6. Is there any evidence that authors measured more outcomes than reported?	CS:	No
	ERG:	No
Comment: assessment based on the CS and full publication.		
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Yes
	ERG:	No
Comment: not true ITT analysis (n=177) but modified ITT analyses (n=176) (all patients who were randomised to study treatment and received at least one dose of study drug), which is increasingly used in industry sponsored trials.[16] The CS states that one participant was excluded because a diagnosis of MPS IVA could not be confirmed (CS, p. 86). Clarification received from the company states that the participant was randomised to the placebo group. PPP (n=152) was used to perform sensitivity analyses for the primary, secondary, composite, and MVV endpoints (CS, p.71). [redacted]		

The CS states that patients 'treated with the weekly dose of elosulfase alfa improved more than those receiving placebo, although the effect was not statistically significant' for the 3MSCT (CS p12). The 3MSCT was not a primary outcome.

MOR-004 was not powered for any tertiary endpoints including pulmonary function measures such as FVC, FEV_1 and MVV. A footnote under CS Table C15 (p. 94) states that as MOR-004 was not powered to detect changes in tertiary outcomes 'details of the statistical tests/p values are therefore not provided for these outcomes, or for the exploratory analyses'.

The CS provided a quality assessment of MOR-005 based on RCT criteria which, as an open-label single dose regimen extension study, can no longer be considered as an RCT and has therefore been quality assessed as a non-RCT together with MOR-007, by the ERG.

Table 4 Company and ERG assessment of trial quality for non-RCTs

		MOR-005	**MOR-007**
Was the cohort recruited in an acceptable way?	CS	NR	Yes
	ERG	Unclear	Yes
Comment: MOR-005: unable to assess without the study protocol - study enrolled 173/175 patients from the MOR-004 RCT.			
Was the exposure accurately measured to minimise bias?	CS	NR	Yes
	ERG	Unclear	Unclear
Comment: unable to assess without the study protocol			
Was the outcome accurately measured to minimise bias?	CS	NR	Yes
	ERG	Unclear	Unclear
Comment: unable to assess without the study protocol. [redacted]			
Have the authors identified all important confounding factors?	CS	NR	Yes
	ERG	Unclear	Unclear
Comment: unable to assess on the information available.			
Have the authors taken account of the confounding factors in the design and/or analysis?	CS	NR	Yes
	ERG	Unclear	Unclear
Comment: [redacted] MOR-007 – still ongoing, no CSR available.			
Was the follow-up of patients complete?	CS	NR	N/A
	ERG	No	No
MOR-005 – interim data. MOR-007 – interim analysis.			
How precise (for example, in terms of confidence interval and p	CS	NR	N/A

values) are the results?	ERG	Unclear	Unclear
Comment: MOR-005 – limited interim results with varying amounts of detail. MOR-007 – interim analysis - limited date reported			

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

As can be seen in Table 4, 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.

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)".

Normalised Urinary KS monitoring

Consultees have suggested that urinary KS monitoring may be less relevant than clinical outcomes, but that it is useful in monitoring anti-drug antibodies. The ERG's clinical experts suggest that KS is a surrogate outcome but can demonstrate if the enzyme is being taken up. Our experts are not aware of any evidence of a correlation with clinical improvement for this outcome.

Other outcome measures

Vision and hearing, and sleep apnoea were not reported in the CS despite being included in the scope. The reason provided for excluding these outcomes is that the impact 'on these particular manifestations is not known' (CS Table A1, p.18). However, the ERG's clinical expert suggests that sleep apnoea is a significant problem and therefore an important outcome. In response to a request for clarification the company provided data on corneal clouding, sleep and audiometry results to the ERG as part of their clarification response.

The CS included additional outcomes on the impact of the treatment on surgery and time to surgery, as well as a range of additional exploratory outcomes (see ERG Table 5). The study was not powered for tertiary outcomes and it is unclear if it was powered for the additional outcomes used in exploratory analysis.

QoL was measured using the MPS HAQ in MOR-004, which is a disease-specific instrument developed to measure disability in patients with MPS over 8 years of age. It should be completed by the parent/care giver for children less than 14 years of age. There is no validated tool to evaluate QoL in MPS IVA. In addition, this was a tertiary outcome and, as previously stated, the trial was not powered to detect statistical differences in these.

Table 5 The measurement of outcomes employed in the clinical assessment of elosulfase alfa in the CS

Outcomes in Scope	Outcomes in CS	Outcome measures
Endurance	Endurance	Primary outcome MOR-004: 6MWT Secondary outcome MOR-004: 3MSCT
Mobility	Mobility	MOR-004: MPS HAQ Other*: wheelchair dependency (PRO pts) Gait (PRO pts) Joint stiffness (PRO pts) Mobility (part of EQ-5D-5L in PRO pts)
Respiratory and	Respiratory and	Tertiary outcomes MOOR-004: FVC, FEV_1, MVV, Cardiac

cardiac function	cardiac function	valve function (echocardiogram)
Growth and development	Growth and development	Secondary outcome MOR-004: Normalised Urine KS *Additional tests for exploratory purpose MOR-004:* Standing height Growth rate Sitting height Length and weight Hearing (measured using audiometry) Corneal clouding (physical examination Radiographic examinations (of cervical and lumbar spine; lower extremity radiographs for patients ≤20 years)
Vision and hearing	Not reported	
Sleep apnoea	Not reported	
Fatigue	Fatigue	MOR-004: reported as AE Other*: fatigue/ stamina (PRO pts)
Pain	Pain	MOR-004: reported as Adverse Event Other*: BPI-SF (PRO pts - adults) APPT (PRO pts – children)
Mortality	Mortality	Reported as Serious AE MOR-004
Adverse effects	Adverse effects	MOR-004 – any AEs (mild, moderate and severe. Reported symptoms: vomiting, pyrexia, headache, nausea, cough, abdominal pain, diarrhoea, oropharyngeal pain, arthralgia, nasopharyngitis, upper respiratory tract infection, abdominal pain upper, fatigue, otitis media, pain in extremity, back pain, dizziness, dyspnoea, gastroenteritis, chills, decreased oxygen saturation and rash).
HRQoL (patients and carers)	HRQoL (patients and carers; surgery)	MOR-004: MPS HAQ (self-care, mobility and caregiver assistance) Other*: EQ-5D-5L (PRO pts) Employment status Quality of life (carers): Caregiving hours/day

* PRO (patient-reported outcomes) patients is a QoL survey.
3MSCT, 3-minute stair climb test; 6MWT, 6-minute Walk Test; AE, Adverse Event; APPT, Adolescent Pediatric Pain Tool; BPI-SF, Brief Pain Inventory Short Form; FEV_1, 1-second forced expiratory volume;
FVC, forced vital capacity; HAQ, health assessment questionnaire; KS, Keratan Sulfate; MVV, Maximum voluntary ventilation.

3.1.6 Description and critique of the company's approach to trial statistics

As previously stated reported outcomes are based on published and unpublished studies. The CS presents supporting data from unpublished studies (for study details see Section 3.1.3), based on small population sizes.

The primary outcome in MOR-004 was the distance covered in the 6MWT at 24 weeks and results for MOR-004 were presented as ITT analysis (CS Table C15, p. 94).

The trial was powered appropriately for its primary outcome.

The secondary outcomes related to other activity (e.g. stair climbing), respiratory or biochemical measures. The selected ANCOVA approach was appropriate for comparing the three different groups in the study.

Tertiary outcomes in MOR-004 were descriptive only, as the trial was not powered to detect changes.

In MOR-004 a pre-specified subgroup analysis was conducted to assess the relative effects according to gender, baseline 6MWT category (≤200 metres and >200 metres), geography (North America, Europe, other), ethnicity (white versus non-white), baseline use of walking aids and age group (5 - 11, 12 - 18, ≥19 years) at baseline. No statistically significant effects were demonstrated, but as previously stated the study was not powered to detect any such effects.

An analysis to determine the effect of treatment on wheelchair use in MOR-004 was conducted. As this was post-hoc, the results should be interpreted with caution.

The manufacturer presents a summary of the efficacy endpoints from MOR-004 in a forest plot (CS, Figure 12, p 96), showing that point estimates in general favour active treatment over placebo, but only the 6MWT demonstrates a confidence interval which excludes no effect.

In the MOR-005 study the CS (p. 105) suggests that the PPP (because of the allowed surgery) and the QW/QW cohort are the most relevant for this evaluation. The PPP was defined as the subset of the ITT population, who were compliant with the protocol, equating to 90% (52/58) of the ITT population. However, for the 6MWT and the 3MSCT the CS presents the results of both ITT and PPP analyses. For urine KS, the CS presents only the ITT results. In addition, results presented were stated as being interim. The ERG notes that the numbers analysed in the PPP were not provided in the CS. These were provided in response to a clarification question and the number of participants included in the PPP were 161 overall for MOR-005, and 52 for the QW-QW cohort. Although the ERG agrees that there is a potential confounding effect of surgery, suggests that both sets of results should be presented for all outcomes.

As previously stated, patients in MOR-005 were allowed surgical interventions for spinal problems unlike in MOR-004. According to the EPAR (p.49) after 72 weeks of treatment,

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 [redacted] participants underwent surgery (although the ERG notes that the text states [redacted] while the breakdown in clarification response Table 8 shows [redacted]). In the QW-QW cohort [redacted] 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 with worse outcomes (i.e. those 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.

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 (Table 6). 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

is 78, but it is unclear how this number was achieved. The number of records screened is stated as 2174, and after excluding 1878, it appears that 296 (rather than 78 as stated) records remained. Also, according to the PRISMA diagram, (CS p. 62) 64 articles were included in the review, yet only 7 main studies carried out by the company are detailed in the results section (CS p. 93 – 119). In the response to the clarification question the company provided the list of 64 'included' articles, and confirmed that these captured a wide range of articles, not just prospective studies.

There does not appear to be any information in the CS about how data were extracted, by whom, or whether there were one or more reviewers.

Of seven studies outlined in the CS results section, two were not considered further in the CS as they are ongoing and interim results are not included in the CS. Additional information summarising AEs is mentioned in the results section (CS p. 120 – 125), but the CS is unclear which studies apart from MOR-004 have contributed to these details. Clarification provided by the company (p. 27) states that it 'includes all patients from MOR-002, MOR-100, MOR-004, MOR-005, MOR-007 and MOR-008 clinical trials who at any point received elosulfase alfa at the proposed dose of 2.0 mg/kg/week'.

The submitted evidence generally reflects the decision problem defined in the CS. Although not all outcomes to meet the NICE scope were submitted in the original CS, these were submitted as part of the ERG's request for clarification. It is stated that 'none of the other elosulfase alfa studies listed compares the technology with any comparator and so fall outside the scope of the decision problem' (CS p. 67). The ERG assumes that this refers to the additional studies.

Table 6 Quality assessment (CRD criteria) of CS review

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes Eligibility criteria are reported (CS p. 61 and 63).
2. Is there evidence of a substantial effort to search for all relevant research?	Yes Search strategies for clinical effectiveness are reported (CS Appendix 1). See ERG report section 3.1.1 for critique.
3. Is the validity of included studies adequately assessed?	Uncertain Quality assessments are presented for MOR-004, MOR-005, MOR-001 and MOR-007 (CS Tables p. 89 - 92]. However, there is no critical appraisal of MOR-002, MOR-100 or MOR-008.

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 46.0 metres (CI 95% 12.6, 47.6) from baseline). 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);

PPP 43.5 (SD 73.63)]. At 72 weeks these participants would have transitioned to once weekly treatment as per the protocol for phase two of the MOR-005 trial, although the exact timing of this transition differed for each participant (see below).

The CS states that additional pre-specified analyses undertaken to investigate the robustness of the primary analysis results, and to explore the uniformity of the overall 6MWT treatment effect across several sub-populations, demonstrated that treatment effects were similar to the overall group, regardless of age, sex, race, or geographic region, or baseline 6MWT category, and consistently supported the 2.0 mg/kg/QW dose regimen. However, it is unlikely that there was enough power to reliably demonstrate a subgroup difference should one exist.

In MOR-005 when analysed by ITT, overall performance on the 6MWT is worse than when analysed by the PPP.

Figure 17 in the CS (p. 105) shows the analysis (repeated measures model) of the 6MWT for the PPP, illustrating the transition of MOR-004 patients in the fortnightly dosing and placebo group from week 24 to 2mg/kg weekly dose of elosulfase alfa during MOR-005. As previously stated, the PPP excluded patients who had orthopaedic surgeries and missed multiple doses of the study drug. It is unclear from Figure 17 and the CS fails to clarify, at which time point all of these patients had changed to the weekly dosing schedule in MOR-005.

[redacted]

Clarification provided by the company confirms this, stating that most patients transitioned between week 48 and week 72. According to the FDA briefing document on elosulfase alfa,[21] at the time of the week 72 assessments almost all patients (163/168) in MOR-005 were receiving weekly dosing (FAD report page 27). Regardless of this and while not achieving the same kind of improvement as the weekly dose treatment group, the transition population at week 72 also showed improvements for the 6MWT. It should be noted that the footnotes for Figure 17 in the CS have been omitted, [redacted]

Endurance as measured by the 6MWT was a secondary outcome in the MOR-002 dose escalation trial. At baseline the CS reported that the mean (SD) distance walked was [redacted]. At the end of the initial dose escalation phase, which included an initial

0.1mg/kg/week dose for 12 weeks and then a 1.0mg/kg/week dose for 12 weeks, the mean change in distance walked was reported to be 16 metres. At the end of the third phase of the treatment escalation, a 12 week period with 2.0mg/kg/week treatment, the mean change in distance walked was reported to be 14 metres. Treatment was then reduced to 1.0mg/kg/week for 36 weeks and at the end of this period the mean change in distance walked was reported to be 4 metres. The ERG is unable to verify these data as there is no publication or CSR available. The CS also reports median change in distance walked on the 6MWT (CS p. 113) but the ERG have not reproduced these here.

In MOR-100, the dose of elosulfase alfa was increased from the 1.0 mg/kg/week that participants in MOR-002 finished on to 2.0 mg/kg/week. The 6MWT was the primary outcome in this study. In the MOR-002 study, the CS reports results for the ITT population at 12 weeks, 24 weeks, 36 weeks, 48 weeks, 60 weeks, and 72 weeks as change from baseline. The CS also reports results for eight participants followed up at the time of the cut-off for the CSR at week 84. The ERG has focused on the 60 week and the 72 week data in these summaries. Interim data can be found in CS Table C22 (p. 116). The data across all time points appears to be positive for the treatment with the exception of the 72 week data where a negative response on the 6MWT change from MOR-002 data was seen. The CS reports (p. 118) that this decline was primarily driven by four participants who had knee surgery prior to the week 72 assessment. At 60 weeks the change from baseline (in MOR-002) was 3.4 metres. At 72 weeks this was -52.7 metres.

Across MOR-002 and MOR-100 studies, the data presented show wide distributions around the mean values and the CS notes that results were heterogeneous as acknowledged by the CHMP. Caution is therefore recommended in the interpretation of these results because of the wide distributions and also because of the different doses given, the small number of participants, and the lack of a comparator group. The ERG agrees with the CS that the results generally appear to be in favour of treatment with the 2.0mg/kg/week dose over the duration of the studies analysed.

Table 7: Summary results for 6MWT

Outcome, follow-up	**Intervention**	**95% CI, p value**
MOR-004	**2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)**	
6MWT distance (metres change from baseline,	22.5	4.0, 40.9; p=0.017

week 24), LS mean difference		
MOR-005, QW-QW cohort	**2.0mg elosulfase alfa/kg/QW ([redacted]**	
6MWT distance (metres change from MOR-004 baseline, week 72), LS mean difference	ITT: 30.1 PPP: 46	12.6, 47.6, p=N/A 27.4, 64.6, p=N/A
MOR-002	**Elosulfase alfa (see below for doses) (n=20)**	
6MWT, metres (change from baseline, 24 weeks)[a]	mean (SD) 16 (72)	
6MWT, metres (change from baseline, 36 weeks)[b], mean (SD)	14 (63)	
6MWT, metres (change from baseline, 72 weeks)[c], mean (SD)	4 (87)	
MOR-100, extension to MOR-002	**2.0mg elosulfase alfa/kg/QW (n=17)**	
6MWT, metres (change from MOR-002 baseline, 60 weeks), mean (SD)	3.4 (93.24)	
6MWT, metres (change from MOR-002 baseline, 72 weeks), mean (SD)	-52.7 (133.78)	

NR, not reported. 6MWT, 6 Minute Walk Test; LS, Least square. NA, not applicable.
[a]at the end of the 0.1mg/kg/week and 1.0mg/kg/week dose escalation phase
[b]at the end of the 2.0mg/kg/week dose phase
[c]at the end of the 1.0mg/kg/week dose reduction phase

Summary of results for 3-minute stair climb test (3MSCT)

As previously stated, the 3MSCT was not standardised across centres, hence results should be interpreted with caution. MOR-004 failed to show a statistically significant improvement in the 3MSCT at 24 weeks in patients being treated weekly with elosulfase alfa compared to those treated with placebo (LS mean change from baseline 1.1; 95% CI -2.1, 4.4; p=0.494).

MOR-005 does show an improvement in the 3MSCT between baseline and 72 weeks in the group receiving weekly elosulfase alfa, for both the PPP and ITT analyses, but without a comparator it is unclear how this differs from the natural history (Table 8). LS mean change from baseline to week 72 for the ITT population was 5.3 (95% CI 2.3, 8.1) stairs per minute and for the PPP was 6.6 stairs per minute (95% CI 3.3, 9.8). It is difficult to ascertain whether these differences are clinically meaningful. However, deterioration over time would be expected due to natural progression of disease without treatment. In the response to the ERG's clarification request, data for the other cohorts of MOR-005 were provided. 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 seen in the QW:QW cohort [QoW:QoW: ITT 5.0 (SD 710.43); PPP 6.5 (SD 9.09)]. At 72 weeks these participants would have transitioned to once weekly treatment as per the protocol for phase two of the MOR-005 trial, although the exact timing of this transition differed for each participant.

In the MOR-002 study, endurance, as measured by change from baseline in the 3MSCT, was reported to be 6 stairs at the end of the initial dose escalation phase (initial 0.1mg/kg/week dose for 12 weeks and then a 1.0mg/kg/week dose for 12 weeks). At the end of the third phase of the treatment escalation, a 12 week period with 2.0mg/kg/week treatment, the mean change in 3MSCT was reported to be 8 stairs. At the end of the treatment reduction period (to 1.0mg/kg/week for 36 weeks; therefore at 72 weeks from baseline) the mean change in 3MSCT was reported to be 10 stairs. [redacted] The CS also reports median change in 3MSCT (CS p. 114), but the ERG have not reproduced these data here.

The pattern of the data across all time points in the MOR-100 study was positive for treatment with elosulfase alfa with the exception of the 72 week data, where a negative response on the 3MSCT change from MOR-002 data was seen. The CS reports (p. 118) that this decline was primarily driven by 4 participants who had knee surgery prior to the week 72 assessment. At 60 weeks the change from baseline (in MOR-002) was 7.9 stairs. At 72 weeks this was -3.3 stairs.

Table 8: Summary results for 3MSCT

Outcome, follow-up	Intervention	95% CI, p value
MOR-004	**2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)**	
3MSCT (stairs/min, change from baseline, week 24), LS mean difference	1.1	-2.1 to 4.4; p=0.494
MOR-005, QW-QW cohort	**2.0mg elosulfase alfa/kg/QW** [redacted]	
3MSCT (stairs/min, change from MOR-004 baseline, week 72), LS mean difference	ITT: 5.3 PPP: 6.6	2.3,8.1; p=N/A 3.3, 9.8; p=N/A
MOR-002	**Elosulfase alfa (see below for doses) (n=20)**	
3MSCT, stairs (change from baseline, 24 weeks)[1], mean (SD) stairs	6 (9)	
3MSCT,stairs (change from baseline, 36 weeks)[2], mean (SD)	8 (14)	
3MSCT, stairs (change from baseline, 72 weeks)[3], mean (SD)	10 (14)	
MOR-100	**2.0mg elosulfase alfa/kg/QW (n=17)**	
3MSCT,stairs (change from MOR-002 baseline, 60 weeks), mean (SD)	7.9 (17.3)	
3MSCT, stairs (change from MOR-002 baseline, 72 weeks), mean (SD)	-3.3 (21.9)	

NR, not reported. 3MSCT, 3 Minute Stair Climb Test. LS, Least square.
[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 normalised urine KS

MOR-004 at 24 weeks shows a statistically significant drop in normalised urine KS compared to baseline in patients being treated with weekly elosulfase alfa compared to those treated with placebo, with a LS mean percent changes of -40.7% (95% CI -49.0, -32.4; p<0.0001) for the ITT population, suggesting a biological effect of the intervention (Table 9). There was a further decrease in normalised urine KS by week 72 in MOR-005 [LS mean percent changes of -54.3% (95% CI -58.3, -50.3)]. The CS states that this demonstrates that elosulfase alfa is capable of breaking down accumulated body and tissue storage of KS (CS p. 99).

In MOR-007, mean percentage change in urine KS levels were measured in 15 children after 2 weeks and 26 weeks treatment with elosulfase alfa, and in 10 of these 15 children with MPS IVA after 52 weeks' treatment (Table 9). It is unclear why results for the remaining 5 children are not presented at 52 weeks. In the publication of these results[14] it is stated that all 15 participants completed the 52 week assessments. As there are no comparative data, the significance of these data is unclear.

Mean change in urine KS was reported in the MOR-002 dose escalation trial. The CS does not present baseline results for this outcome, but these can be seen in the CSR where it was reported that [redacted] At 24 weeks (after a 12 week 0.1mg/kg/week and a 12 week 1.0mg/kg/week dose) the mean change was reported to be -9µg/mg. After the 12 week period with 2.0mg/kg/week treatment (i.e. at 36 weeks), the mean change was reported to be -13µg/mg. At the end of the reduced treatment period (1.0mg/kg/week for 36 weeks, therefore at 72 weeks) the mean change was reported to be -10µg/mg. The CS also reports median change in urine KS (CS p. 114), but the ERG have not reproduced these data here.

In the MOR-100 extension study urine KS decreased across all time points. At week 60 the percent decrease was 43.7% and at week 72 this was 35.1%.

Table 9: Summary results urine KS

Outcome, follow-up	Intervention	95% CI, p value
MOR-004	**2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)**	
Normalised urine KS (% change from baseline, week 24), LS mean difference	ITT: -40.7	-49.0, -32.4; p<0.0001
MOR-005, QW-QW cohort	**2.0mg elosulfase alfa/kg/QW**	

	[redacted]	
Normalised urine KS (% change from MOR-004 baseline, week 72), LS mean difference	ITT: -54.3 [redacted]	-58.3, -50.3; p=N/A [redacted]; 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 [redacted] (change from baseline, 24 weeks)[1]	-9 (8) [redacted]	
Mean (SD) µg/mg [redacted] (change from baseline, 36 weeks)[2]	-13 (9) [redacted]	
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: [redacted] 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]

MVV

Differences in MVV percentage change from baseline appear to favour the weekly elosulfase alfa treatment (ERG Table 10) 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].

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 10 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	10.3 (PPP; [redacted][1])	-1.8, 22.4; p=0.0943 (ITT)[2]
MOR-005, QW-QW cohort	**2.0mg elosulfase alfa/kg/QW ([redacted])**	
MVV (% change from MOR-004 baseline, week 72), LS mean[3]	[redacted][1]	[redacted][1]
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 [redacted] [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 (Table 11), 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.

The CS presents no separate long-term data from MOR-005 for this outcome, instead reporting FVC as part of a composite outcome. [redacted].

In the MOR-002 study data were presented for the 72 week data collection point only for this tertiary outcome. The mean percentage increase from baseline in FVC was reported to be 12.5%. The ERG is unable to verify these data.

In MOR-100 at 72 weeks the FVC showed a 16.1% increase from MOR-002 baseline.

Table 11 Changes in FVC

Outcome, follow-up	Intervention/s	95% CI, p value
MOR-004	**2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)**	
FVC (% change from baseline, week 24), LS mean	PPP 3.3 [redacted]	-3.1, 9.6; p=0.3041 (ITT)[2]
MOR-005, QW-QW cohort	**2.0mg elosulfase alfa/kg/QW** [redacted]	
FVC (% change from MOR-004 baseline, week 24), LS mean[3]	[redacted]	[redacted]
MOR-002	**Elosulfase alfa variable doses over 72 weeks (n=20)**	
FVC (% increase from baseline, 72 weeks), mean	12.5%	
MOR-100	**2.0mg elosulfase alfa/kg/QW (n=17)**	
FVV (% increase from baseline, 72 weeks), mean (SD)	16.1% (21.96)	

[1] Source MOR-005_CSR [redacted] [2] not powered for statistical comparison.
[3] Repeated Measures ANCOVA of percent changes from baseline with terms baseline MVV, treatment, timepoint, 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.

FEV_1

The point estimate of the FEV_1 percentage change from baseline appears to favour the weekly elosulfase alfa treatment when compared to placebo in MOR-004 at 24 weeks (1.8%; CI -5.5, 9.2), as illustrated in CS Figure 12 (p. 96). Although no p-value is provided, the CS states that results for tertiary endpoints were not statistically significant (p. 12). Neither the CS nor the CSR presents separate long-term data from MOR-005 for this outcome (Table 12).

In the MOR-002 study, data were presented for the 72 week data collection point only. The mean percentage increase from baseline in FEV_1 was reported to be 8.4%. The ERG is unable

to verify these data. The CS also reports results at 72 weeks for the total lung capacity, the forced inspiratory vital capacity and the forced expiratory time. Mean percentage changes from baselines were reported to be 10.1%, 18.7% and 61.7% for these three outcomes respectively.

Table 12 Changes in FEV_1

Outcome, follow-up	Intervention/s	95% CI, p value
MOR-004	**2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)**	
FEV_1 (% change from baseline, week 24), LS mean	1.8	-5.5, 9.2; p=NR
MOR-005, QW-QW cohort	**2.0mg elosulfase alfa/kg/QW (n=56)**	
FEV_1	NR	
MOR-002	**Elosulfase alfa variable doses over 72 weeks (n=20)**	
FEV_1 (% increase from baseline, 72 weeks), mean	8.4%	

LS, least square. NR, not reported.

Summary of results for composite outcome (6MWT/3MSCT/MVV)

Due to the inconsistency of the measurement of the 3MSCT (discussed above), any composite measure including it should be treated with caution. The analysis of the composite endpoint for the ITT population (combining changes from baseline in 6MWT, 3MSCT and MVV z-scores equally weighted) was stated as pre-specified in the CS, but it is not clear if this was pre-specified or when it was pre-specified. While results showed a close to statistical significance difference for the elosulfase alfa group compared with the placebo group (p=0.053), the study was only powered to detect differences for the 6MWT (Table 13).

Table 13: Composite outcome (6MWT/3MSCT/MVV)

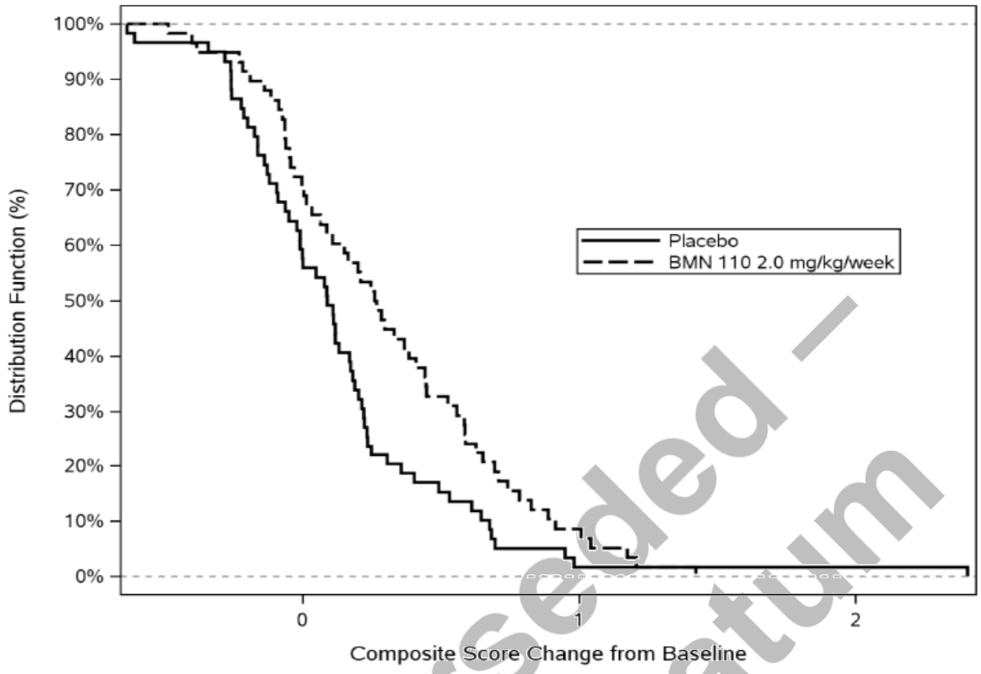
Outcome, follow-up	Intervention Dose	95% CI, p value
MOR-004	**2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)**	
6MWT/3MSCT/MVV composite z-score (% change from baseline, week 24), LS mean difference	ITT: 0.1	0.0, 0.3; p=0.053

NR, not reported.

Summary of results for responder analysis

MOR-004 assessed response to treatment by considering a cumulative distribution function in the placebo and elosulfase alfa 2.0 mg/kg groups. Figure 1 is reproduced from the CS (CS Figure 14, p. 98). This shows that for the majority of thresholds in a composite endpoint of 6MWT, 3MSC and MVV, a higher proportion of patients in the elosulfase alfa group compared

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. The majority of patients responding (33/56) exhibit a response in both domains ([redacted]), showing improvements in both pulmonary function and endurance (Table 14). 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] 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 (Table 15).

Table 14 Frequency Counts of response on endurance and breathing from baseline to week 72 (MOR-005 PPP, QW/QW Cohort)

Analysis Time Point	Category	No. of patients	Percentage (%)
Week 72 (MOR-005 week 48)	Multi-domain responder[1]	[redacted]	[redacted]
	Single-domain responder[2]	[redacted]	[redacted]
	Non-responder[3]	[redacted]	[redacted]

Source: [redacted] (CS Table C18, p106).
[1] Multi-domain responders: subjects with positive change from baseline in endurance (as measured by 6MWT or 3MSC) and breathing (as measured by MVV or FVC); [2] Single-domain responders: subject with positive change from baseline in either endurance (6MWT or 3MSC) or breathing (MVV or FVC) only; [3] Non responder: subject with positive change from baseline in none of 6MWT, 3MSC, and (MVV or FVC).

Table 15 Descriptive statistics for change from baseline in 6MWT and FVC for subset to response on endurance and breathing from baseline to week 72 (MOR-005 PPP; QW/QW Cohort)

Analysis Time Point	Category	6MWT (n), Mean (SD) [Median]	FVC (n), Mean (SD) [Median]
Week 72 (MOR-005 week 48)	Multi-domain responder[1]	[redacted]	[redacted]
	Single-domain responder[2]	[redacted]	[redacted]

Source: [redacted] (CS Table C19, p106).
[1] Multi-domain responders: subjects with positive change from baseline in endurance (as measured by 6MWT or 3MSC) and breathing (as measured by MVV or FVC); [2] Single-domain responders: subject with positive change from baseline in either endurance (6MWT or 3MSC) or breathing (MVV or FVC) only.

Summary of results for height and growth rate z-scores

Normal standing height and growth rates appear to be better (i.e. greater standing height and increased growths) in MPS IVA patients treated with weekly elosulfase alfa at week 24 of MOR-004 compared to those treated with placebo, although no longer term data in support of this is reported for MOR-005. While MOR-004 was not powered for a statistical comparison of these outcomes, p-values were reported but not statistically significant (Table 16). The ERG notes that the meaningfulness of these outcomes are uncertain and longer term data would be needed in order to draw any conclusions.

The interim results of MOR-007 show the mean growth of children with MPS IVA <5 years and ≥2 years receiving elosulfase alfa over 52 weeks (Table 16). Although 15 children were included in the study (CS Table C21), 52 week results are given for 10 children (see above). There are discrepancies in the baseline figures in Tables CS App2 (standing height n=13) and CS App3 (standing height n=12) because one child <2 years old may have been excluded from calculations to allow for calculation of age-related z-scores. The company compared the mean growth of children in MOR-007 to an untreated cohort of the same age-range from MOR-001. These findings suggest that elosulfase alfa may slow the rate of deviation from normal growth rates seen in untreated children with MPS IVA. However, the comparison group was

retrospective and larger than the intervention group, reducing confidence that there were no differences between the two groups that may have affected this outcome.

In the MOR-002 dose escalation study mean anthromorphic measurements (tertiary outcomes) at the end of 72 weeks were reported in the CS to have increased from baseline. The length had increased by 5.3cm, sitting and standing height by 2.3cm and weight by 2.6kg. The CS also reported right knee mean height and left knee mean height but the ERG has not reproduced these data here. The ERG is unable to verify these data.

Table 16 Changes in normalised height and growth rate z-scores

Outcome, follow-up	**Intervention/s**		**Treatment effect (95% CI); p value**
MOR-004 (change from baseline, week 24) Males ≤18 years, females ≤15 years	**2.0mg elosulfase alfa/kg/QW (n=58)**	**Placebo (n=59)**	**(Intervention vs Placebo)**
Normalised standing height z-score, LS mean change (SD)	0.0 (0.06)	-0.2 (0.06)	0.1 (0.0, 0.3); p=0.1149*
Normalised growth rate z-score, LS mean change (SD)	0.5 (0.16)	0.2 (0.18)	0.4 (-0.1, 0.9); p=0.1032)*
MOR-005, QW-QW cohort			
NR			
MOR-007 (change from baseline, week 52 – interim data) Boys and girls <5 years at baseline	**2.0mg elosufase alfa/kg/QW (n=10)**		
Mean change in centimetres from baseline (SD) % change from baseline (SD)	5.3 (2.35) 5.9% (2.53)		N/A
Mean change in height/length for age z-scores from baseline (SD)	-0.4 (0.53)		N/A

* not powered for statistical comparison. LS, least square. NR, not reported, N/A, not applicable.

Summary of results for weight

The results of MOR-007 show the mean weight gain of 10 children with MPS IVA <5 years and ≥2 years receiving elosulfase alfa over 52 weeks (

Table 17). However, no comparative data are given, either to children with MPS IVA not treated with elosulfase alfa or to z-scores of children with normal growth. Conclusions about the effect of the drug on outcomes can therefore not be made.

Table 17 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 elosufase alfa/kg every week (n=10) - No comparator**	
Mean change from baseline in kilograms (SD) % change from baseline (SD)	1.7 (0.81) 13.8% (7.33)	N/A

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 18). 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 18); it shows no patients as wheelchair dependent at baseline and 2 patients being wheelchair dependent at week 72.

The CS states that [redacted] 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 72) 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 18 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	[redacted]	[redacted]	[redacted]
Sometimes wheelchair	[redacted]	[redacted]	[redacted]
Always wheelchair	[redacted]	[redacted]	[redacted]

*Source: MOR-005 CSR, Data on File.

Summary of results for orthopaedic surgery

Despite surgery being excluded in MOR-004, some operations were performed in the course of the trial and estimates from CS Figure 18 (CS p. 108) would suggest this to have occurred in around 2% of patients in the 2.0mg elosulfase alfa/kg/QoW group. In MOR-005, orthopaedic surgery at week 72 occurred less in those receiving weekly elosulfase alfa compared to those receiving placebo (8% vs 18% respectively). The preliminary data seems to offer support to treatment with weekly elosulfase alfa reducing or possible delaying the need for surgery in patients suffering from MPS IVA as suggested in the in the EPAR of the CHMP (Table 19).

Table 19 Orthopaedic surgery

Outcome, follow-up	**Intervention/s**		**p value**
MOR-005	**2.0mg elosulfase alfa/kg/QW (n=58)**	**Placebo (n=59)**	
Orthopaedic surgery week 72 (MOR-005 week 48), %	8	18	NR

NR, not reported.

Summary of vision, hearing and sleep apnoea, (data from clarification response)

In the company's clarification response, it is stated that weekly elosulfase alfa compared with placebo at the end of MOR-004 (week 24) showed no apparent change in corneal health according to investigator assessment of 'presence' or 'absence' of clouding (no definitions provided). Data provided in the clarification response are without the results for the placebo group of MOR-004. However, the ERG was able to check the data from the CSR (provided by the company upon request by the ERG). The reported data for MOR-004 however, is for the two subsequent treatment cohorts from MOR-005 (summarised here for QW-QW in ERG Table 21). At the end of MOR-005, [redacted] receiving the weekly elosulfase alfa (QW/QW group) with corneal clouding at baseline no longer had clouding at week 72. The company states that this appears to suggest that treatment with elosulfase alfa at the licensed dose may halt or even reverse corneal clouding (often present in MPS IVA patients), although results should be interpreted with caution given the lack of a control group. In contrast, data appears to show that [redacted] without corneal clouding at baseline appear to have corneal clouding at week 72. The ERG notes that these may be post-hoc analyses; that there is no comparator

group for the MOR-005 QW-QW observed data (although the company states that all patients in the QOW:QOW group continued to have corneal clouding at week 72); that it is unclear what definitions were used for the outcomes and how reliable these are; and no statistical testing for differences between the MOR-004 treatment groups is reported.

Table 20 Corneal clouding evaluation shift (ITT population)

	Baseline	
	QW-QW (n=58)	
Week 24 [MOR-004 (MOR-005 Week 0)]	**Absent**	**Present**
Absent	[redacted]	[redacted]
Present	[redacted]	[redacted]
Week 72 (MOR-005 Week 48)	**Absent**	**Present**
Absent	[redacted]	[redacted]
Present	[redacted]	[redacted]

Source: Table 1 Clarification document (p. 2)

As noted by the company, audiometric measurements from MOR-004 on hearing ability at various thresholds and frequencies were based on a very small number of patients (see ERG Table 21). Compared with placebo, patients receiving elosulfase alfa 2.0mg/kg/week were reported to have 'numerically improved hearing' in the left ear at week 24 at each frequency apart from the lowest (500 Hz), and decreased hearing in the right ear at each frequency. However, these data need to be interpreted with caution owing to the small sample sizes and therefore lack of any formal statistical testing for differences, and limited details as to the hearing tests given. The company note the limitations of these data.

Table 21 Audiometry results MOR-004

Parameters, mean (SD)	**Elosulfase alfa 2.0mg/kg/week (n=7/58)**		**Placebo (n=9/59)**	
	Baseline	**Week 24**	**Baseline**	**Week 24**
Left Ear				
Left Ear Frequency Level 500 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Left Ear Frequency Level 1000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Left Ear Frequency Level 2000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Left Ear Frequency Level 4000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Left Ear Frequency Level 6000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Left Ear Frequency Level 8000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Right Ear				
Right Ear Frequency Level 500 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Right Ear Frequency Level 1000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Right Ear Frequency Level 2000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]

Right Ear Frequency Level 4000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Right Ear Frequency Level 6000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]
Right Ear Frequency Level 8000 HZ, bel	[redacted]	[redacted]	[redacted]	[redacted]

Source: Appendix 1 Clarification document (p. 28 - 35).

Results for sleep apnoea outcomes for a modified ITT population of one study (MOR-008) were provided in response to the ERG's clarification request. The ERG clinical advisors suggest that this is an important outcome. Outcomes were reported as the number of blood oxygen de-saturations ≥3% per hour, the minimum blood oxygen saturation and number of respiratory events per hour. As discussed by the company, the results show no clear trends in change from baseline to week 24 in any of these outcomes (Table 22).

Table 22 Home sleeping test results MOR-008 (mITT population)

	2.0 mg/kg/wk		
Parameter, mean (SD)	**Baseline** [redacted]	**Week 24** [redacted]	**Week 24 mean change from baseline (min, max)** ([redacted]
AHI, events/hour	[redacted]	[redacted]	[redacted]
Minimum O_2 saturation, %	[redacted]	[redacted]	[redacted]
Desaturations, ≥3% per hour	[redacted]	[redacted]	[redacted]
REI, events/hour	[redacted]	[redacted]	[redacted]

Source: Table 2 Clarification document (p. 3).
AHI, Apnoea /Hypopnea Index. REI, Respiratory Event Index.

Summary of health related quality of life (HRQoL)

QoL in MOR-004 was assessed using the MPS HAQ. The HAQ results for caregiver assistance and mobility domains appear to favour those treated with weekly elosulfase alfa at week 24 of MOR-004 in the ITT population compared with placebo as illustrated in CS Figure 12 (CS p. 96). The estimated treatment effect (mean difference) for caregiver assistance (reduction in assistance) was -0.91 (CI 95% -2.8, 1.1) and -0.31 (CI 95% -0.8, 0.3) for mobility domains (improvement in dexterity, mobility, walking, stair climbing, and gross motor skills), with negative values denoting an improvement (ERG Table 23). While the trial was not powered for a statistical comparison of these outcomes, p-values were reported but not statistically significant (0.39 and 0.34, retrospectively). However, there was no improvement in the Self-Care domain (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting) of the HAQ for those treated with weekly elosulfase alfa at week 24 in MOR-004 compared to those treated with placebo (estimated treatment effect of 0.1; CI -0.3, 0.5; p=0.74). The CS suggests that one-quarter of the questions in the Self-Care domain were felt to be irrelevant or insufficiently specific to assess activities of daily living for people with MPS IVA (CS p. 101), which was not

the case for the other two domains. While the results may be clinically relevant to patients, no long-term data from MOR-005 was presented in support.

Table 23 Changes in MPS HAQ

Outcome, follow-up	Intervention	95% CI, p value
MOR-004	**2.0mg elosulfase alfa/kg/QW (n=58) vs placebo (n=59)**	
MPS HAQ (% change from baseline, week 24)		
Self-care domain score, LS mean difference	ITT 0.1[1]	-0.3, 0.5; p=0.74[2]
Caregiver assistance domain score, LS mean difference	ITT -0.91[1]	-2.8, 1.1; p=0.39[2]
Mobility domain score, LS mean difference	ITT -0.31[1]	-0.8, 0.3; p=0.34[2]
MOR-005	**2.0mg elosulfase alfa/kg/QW**	
MPS HAQ	NR	

ITT, intention-to-treat analysis. LS, least square. NR, not reported.
[1] Negative values represents an improvement. [2] not powered for statistical comparison.

Subgroup analyses results

MOR-004 presents the results of the 6MWT in various subgroups (CS, Figure 14): sex, 6MWT result at screening > 200m, Region (North America, Europe, Other), Race (White, non-White), Use of a waling aid at baseline, age group (5-11 years, 12-18 years, >19 years).

In general the point estimates for all groups are in favour of the active treatment rather than placebo, but few subgroups (Screening 6MWT ≤ 200m; Race: White; Use of walking aid as baseline; age group: 12-18 years) have confidence intervals which exclude no effect.

No subgroups show a statistically significant difference in effect when compared with other subgroups in the same category.

Summary of adverse events (AE)

The CS states that there were no side effects leading to the permanent discontinuation of the treatment and no deaths in connection with the treatment, although as can be seen in Table 24, 22% of patients receiving a weekly dose of elosulfase alfa are categorised as having experienced ‘any AE leading to permanent study drug discontinuation’. Two patients receiving weekly elosulfase alfa experienced AEs that led to dose interruption/discontinuation requiring medical attention. The CS states that in the proposed dose population (results from 6 clinical

studies), 14% of patients had AEs during infusion that required infusion interruption or discontinuation as well as medical intervention to treat the event.

In MOR-004, the most common AEs during treatment with weekly elosulfase alfa were associated with infusions and included vomiting (45%), pyrexia (43%) and headache (21%). While most patients experienced at least 1 infusion associated reaction (IAR) (MOR-004: 90% weekly elosulfase alfa and 92% placebo; proposed dose population: 71%), the CS states that all patients received and tolerated subsequent infusions. The frequencies of IARs were reported to be generally higher during the first 12 weeks of treatment, tending to occur less frequently with duration of treatment.

Table 24 Incidence in ≥10% AEs for MOR-004 and by Proposed Dose Population

Adverse Event (AE), n (%)[1]	**Incidence (MOR-004 Safety Population), n (%)**		**PDP - Incidence: n (%) Annualised frequency: mean events/subject year**
	Elosulfase alfa 2.0 mg/kg/QW n = 58	**Placebo n = 59**	**>48[2] (n=52)**
≥ 1 reported AE			42 (80.8) 11.68
Any AE	56 (96.6)	57 (96.6)	
Mild	28 (48.3)	36 (61.0)	
Moderate	26 (44.8)	20 (33.9)	
Severe	2 (3.4)	1 (1.7)	
Any study drug-related AE[3]	42 (72.4)	36 (61.0)	
Mild	24 (41.4)	32 (54.2)	
Moderate	16 (27.6)	4 (6.8)	
Severe	2 (3.4)	0	
Any AE leading to dose interruption/discontinuation requiring medical attention[3]	2 (3.4)	0	
Any AE leading to permanent study drug discontinuation[3]	13 (22.4)	0	
Vomiting	26 (44.8)	21 (35.6)	15 (28.8) 0.98
Pyrexia	25 (43.1)	17 (28.8)	14 (26.9) 0.82
Headache	24 (41.4)	21 (35.6)	13 (25.0) 0.96
Nausea	18 (31.0)	12 (20.3)	4 (7.7) 0.22
Cough	16 (27.6)	21 (35.6)	9 (17.3) 0.21
Abdominal pain	14 (24.1)	5 (8.5)	2 (3.8) 0.43
Diarrhoea	12 (20.7)	7 (11.9)	9 (17.3) 0.23
Oropharyngeal pain	12 (20.7)	7 (11.9)	3 (5.8) 0.28
Anthralgia	10 (17.2)	17 (28.8)	5 (9.6) 0.06
Nasopharyngitis	10 (17.2)	9 (15.3)	7 (13.5) 0.27
Upper respiratory tract infection	10 (17.2)	9 (15.3)	3 (5.8) 0.33
Abdominal pain upper	9 (15.5)	5 (8.5)	6 (11.5) 0.16
Fatigue	9 (15.5)	15 (25.4)	5 (9.6) 0.14
Otitis Media	9 (15.5)	4 (6.8)	
Pain in extremity	9 (15.5)	9 (15.3)	5 (9.6) 0.31
Back Pain	7 (12.1)	6 (10.2)	

Dizziness	7 (12.1)	3 (5.1)	
Dyspnoea	7 (12.1)	3 (5.1)	
Gastroenteritis	7 (12.1)	4 (6.8)	
Chills	6 (10.3)	1 (1.7)	
Decreased oxygen saturation	6 (10.3)	6 (10.2)	
Rash	6 (10.3)	5 (8.5)	6 (11.5) 0.22

PDP, Proposed Dose Population. Severity categories: mild, no limitation of usual activities; moderate, some limitation of usual activities; severe, inability to carry out usual activities (from trial publication).
[1] Data from Table C23 and C24 (CS p. 120 - 123). [2] Weeks 49 to 100. [3] Data from trial publication (classified as possibly or probably related to study drug).

At least one serious adverse event (SAE) occurred in nearly 16% of patients receiving weekly elosulfase alfa at 24 weeks in MOR-004, increasing to 24% in the proposed dose population at >48 weeks (Table 25).

Hypersensitivity AEs occurred in 20.7% (data from trial publication) of the patients treated weekly with elosulfase alfa in MOR-004, leading to two infusions that had to be interrupted and one infusion that could not be completed. The CS suggests that hypersensitivity reactions appear not to be dose dependent, with no change over time in incidence of hypersensitivity reactions.

The CS states that relative risk, risk difference and confidence interval information for AE data is not available (CS p. 121).

Table 25 SAEs for MOR-004 and by Proposed Dose Population

SAEs, n (%)	**Incidence (MOR-004 Safety Population), n (%)[1]**		**PDP - Incidence: n (%) Annualised Frequency: mean events/subject year[2]**
	Elosulfase alfa 2.0 mg/kg/QW n = 58	**Placebo n = 59**	**>48[3] (n=86)**
Patients with ≥ 1 reported SAE	9 (15.5)	2 (3.4)	21 (24.4) 0.52
Knee deformity			5 (5.8) 0.11
Poor venous access			1 (1.2) 0.02
Otitis media	1 (1.7)	0	(1.2) 0.01
Central venous catheterization			1 (1.2) 0.01
Medical device implantation			2 (2.3) 0.01
Pneumonia	2 (3.4)	0	0
Hypersensitivity	1 (1.7)	0	0
Infusion site reaction/site pain	1 (1.7)	0	2 (2.3) 0.02
Joint dislocation			1 (1.2) 0.03
Knee operation			2 (2.3) 0.01
Medical device removal			2 (2.3) 0.05
Pyrexia			2 (2.3) 0.01
Urticaria	1 (1.7)	0	

Viral upper respiratory tract infection	1 (1.7)	0	
Vomiting	1 (1.7)	0	
Cervical cord compression	0	1 (1.7)	
Deafness	0	1 (1.7)	

Severity categories: mild, no limitation of usual activities; moderate, some limitation of usual activities; severe, inability to carry out usual activities (from trial publication).
[1] Data from trial publication. [2] Data from Table C25 (CS p. 123 - 124). [3] Weeks 49 to 100.

The CS (p112) presents a summary of AEs from MOR-007. It is stated that 11 out of 15 participants (73.3%) experienced at least one study drug-related AE up to the 52 week interim results. The most commonly-reported were pyrexia (40.0%) and vomiting (33.3%). Eight serious AEs occurred in 4 children, including 1 case of elosulfase-related hypersensitivity. Three participants (20.00%) had infusions that were interrupted or discontinued due to an AE requiring medical intervention. Six out of 743 infusions (0.8%) administered led to AEs requiring interruption and medical intervention with IV antihistamines and/or IV steroids. Additional AE data appears in a poster presentation of the interim results. [14] However, the ERG anticipated that the company may have included the MOR-007 results in the proposed dose population (Table 17), so further details are not presented in the ERG report.

Longer-term data would be necessary to evaluate the extent and severity of AEs. It is unclear to the ERG what the timelines of the reported AEs are because of the different durations of the included studies in the proposed dose population.

3.4 Summary

The CS present evidence from a range of studies, including one RCT which compared two different dosing schedules of elosulfase alfa with placebo (the ERG only reports on the licenced dose of elosulfase alfa i.e. 2.0mg/kg/weekly). This trial, MOR-004, which had a 24-week duration, was relevant to the decision problem. Results of this trial showed that weekly doses of 2.0mg/kg elosulfase alfa led to statistically significant improvements in the primary outcome (6MWT) when compared with placebo. This is a surrogate outcome and the ERG agrees that this is a reasonable outcome to assess patient endurance, a key patient outcome, given the nature of the condition. The ERG notes that there is a placebo effect on the 6MWT, which the CS does not make reference to. The placebo effect may be related to issues with the approach to the assessment of the measure. For example, it has been documented that the 6MWT can be subject to differences due to the encouragement of the person administrating the test. Despite this apparent placebo effect, the results do suggest that there is a treatment effect of the weekly

dose of treatment. The CS reports that the difference in 6MWT is a clinical-relevant change, and although there does not appear to be any evidence to support this empirically, the CHMP and the ERG clinical advisors suggest that the difference in 6MWT is a meaningful difference. On other outcomes reported in the MOR-004 RCT, the CS reports that there were 'trends' in favour of the treatment. The ERG notes that these results are not statistically significant and the interpretation that there is a 'trend' in favour of treatment is misleading. Confidence intervals for secondary and tertiary outcomes in the trial were in most cases crossing the line of no effect (for example see CS Figure 12, p. 96).

The CS also presents data from an extension study to the 24-week RCT, the MOR-005 study. This study is useful in that it reports data for a longer-period of time than the trial, however, the study design did not include a comparator group and therefore treatment effects seen need to be interpreted cautiously. In addition, results are interim and the CS states that only results from one cohort are meaningful to the decision problem (this was from participants who had received 2.0mg/kg/week throughout the 24 weeks of MOR-004 and 48 weeks of MOR-005). Although the ERG agrees this is the most relevant cohort, the company provided results from the other cohorts in response to a request for clarification, which has been helpful in considering the results of the presented cohort. The presentation of results included those from an ITT population and those from a PPP because of the potential for surgical procedures being a confounder. The ERG view is that there is quite a difference in outcomes between the ITT and PPP analysis and that the ITT analysis is more representative of the patient group. Results show that improvements on 6MWT and 3MSCT were sustained longer term, although, without a comparator group and the potential for a placebo effect, it is unclear exactly how reliable the effects seen are.

[redacted]

Supporting data were presented from two other clinical studies. An uncontrolled study (interim results) in a younger paediatric group (aged <5 years) showed gains in objective outcomes such as height and weight measures when compared retrospectively with evidence from a natural history study. A further uncontrolled study, which was an initial dose escalation study followed by a further extension study, showed that in general, outcomes improved from baseline over the

72-week period of study. Results from this study were predominantly to ascertain the licensed dose of elosulfase alfa and therefore need to be interpreted cautiously. Two other studies have been undertaken by the company, but no results were presented in the CS.

AEs were presented for the MOR-004 trial and for a 'proposed dose population' defined as participants from any of the 6 clinical studies included in the marketing authorisation application who were treated with elosulfase alfa at 2.0 mg/kg/week (n=222 for periods ranging from 1 week to 100 weeks) (CS p. 121). The CS does not provide any narrative around the AEs seen in the MOR-004 trial. The ERG note the rate of any AEs in MOR-004 were in the region of 97% in both the treated and placebo groups, although the majority of these were mild or moderate in severity. Drug-related AEs were seen in 61% of the placebo group and 72% of the elosulfase alfa 2.0mg/kg/week group. In the pooled data from 6 studies, approximately 80% reported at least one AE. The most common of those reported were vomiting and pyrexia. The severity of these events was not reported by the CS.

4 ECONOMIC EVALUATION

4.1 Overview of the company's economic evaluation

The company submission to NICE includes:

i) A review of published economic evaluations of the treatment of MPS IVA.
ii) A report of an economic evaluation undertaken for the NICE HST process. The costs and health effects of elosulfase alfa are compared with current clinical management without elosulfase alfa for people with MPS IVA.

Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations of treatment of MPS IVA. See section 3.1 of this report for the ERG critique of the search strategy.

The inclusion and exclusion criteria for the systematic review are listed in section 10.1.5 of the CS (p. 149). The inclusion criteria state that analyses of cost effectiveness, cost utility or cost minimisation of Vimizim®, elosulfase alfa, BMN 110 in people with MPS IVA would be included. The exclusion criteria state that studies in languages other than Polish, English, German and French would be excluded. The search also includes HRQoL studies. One HRQoL study was

identified from screening 13 titles and abstracts. No economic evaluations were included for full review.

CEA Methods

The cost consequence analysis uses a Markov model to estimate the costs and health effects of elosulfase alfa compared with current clinical management without elosulfase alfa in people with MPS IVA.

The Markov model consists of six main health states: asymptomatic, no wheelchair use, some wheelchair use, wheelchair-dependent, paraplegic health state, end stage (and a death health state), and a 1 year cycle. The analysis is conducted from an NHS perspective and consists of a lifetime horizon. The starting population is the MOR-001 population,[15] which is used as a proxy for the prevalent population in England. Patients' progression through the model is based upon time to symptom development, change in wheelchair use, change in 6MWT and change in FVC.

The economic evaluation makes the following assumptions: patients treated with elosulfase alfa would have a 5-year delay in transition from the asymptomatic state to the no use wheelchair health state; there is a 2-year duration in end-stage health state for all patients; elosulfase alfa treated patients would have quicker recovery rates form surgery compared to untreated patients; treated patients in each health state have improved HRQoL compared to untreated patients; patients with elosulfase alfa have reduced mortality compared to treated patients; there is a slowed rate of progression of disease in multi-domain and single-domain responders, where multi-domain responders are assumed not to progress (assumptions listed in CS Table D2, p. 164).

The transition probabilities between health states are based on the change in wheelchair use (for first cycle only) and decline in 6MWT and FVC (for subsequent cycles). Treatment effectiveness is based upon the MOR-005 study[10] for change in wheelchair use and the MOR-004 trial[9] for changes in 6MWT and FVC. Mortality is implemented as a relative risk compared to the normal population for the treated and untreated groups (CS p. 171).

HRQoL is included in the model through the use of utility values assigned to each health state. These values were obtained from a burden of illness study for MPS IVA[8] and clinical opinion. In

addition, there is assumed to be a disutility for caregivers according to health state. These disutilities were based upon published values estimated for carers of people with multiple sclerosis (MS).

Costs are included for intervention (drug costs), administration costs, health state costs, surgery costs, and caregiver costs. Resource use was estimated by clinical experts. Health state costs were taken from NHS reference costs 2011-12.

Sensitivity analyses were conducted on parameter estimates and additional scenario analyses were modelled.

CEA Results

Results are presented below in Table 26 below as discounted costs and QALYs (CS Table D29, p. 203); life years are also reported.

Table 26: Base case results (discounted) (reproduced from CS Table D29 p.203)

	Costs	Incremental costs, £	QALYS	Incremental QALYs
Standard treatment	£618,812	-	9.75	-
Elosulfase alfa	[redacted]	[redacted]	27.93	18.18

The CS also presents probabilistic sensitivity analyses for different willingness to pay thresholds (results presented in CS Figure 36 p. 211).

The CS states that the cost consequence analysis presented demonstrates very substantial QALY gains for MPS IVA patients treated with elosulfase alfa.

4.2 Critical appraisal of the company's submitted economic evaluation

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 27 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[22]). Overall the company has followed recommended methodological guidance.

Table 27 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well-defined question?	Yes	
Is there a clear description of alternatives?	Yes	
Has the correct patient group / population of interest been clearly stated?	Yes	*(Discussed in sections 4.2.2)*
Is the correct comparator used?	Yes	
Is the study type reasonable?	Yes	
Is the perspective of the analysis clearly stated?	Yes	
Is the perspective employed appropriate?	Yes	*Discussed in sections 4.2.6/4.2.7 for costs and4.2.5 for outcomes)*
Is effectiveness of the intervention established?	Yes	Treatment effectiveness shown for 24 week RCT MOR-004 for elosulfase alfa versus placebo
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	*(Discussed in section 4.2.1)*
Are the costs and consequences consistent with the perspective employed?	Yes	*(Discussed in sections 4.2.6/4.2.7 for costs and4.2.5 for outcomes)*
Is differential timing considered?	Yes	*(Described in section 4.1. Discussed in section 4.2.1)*
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	(*Described in section 4.1. Discussed in section 4.2.9)*

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in ERG Table 28.

Table 28 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	*Discussed in section 4.2.3)*
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	*(Discussed in section 4.2.5)*
Type of economic evaluation: Cost effectiveness analysis	Yes	Referred to as a cost consequence model.

Synthesis of evidence on outcomes: Based on a systematic review	Yes	*Discussed in section 0)*
Measure of health benefits: QALYs	Yes	*(Discussed in section 4.2.5)*
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	*(Discussed in section 4.2.5)*
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes	*(Discussed in section 4.2.5)*
Source of preference data: Representative sample of the public	Yes	*(Discussed in section 4.2.5)*
Discount rate: 3.5% pa for costs and health effects	No	Costs and health effects discounted at 1.5%

? = uncertain. N/A, not applicable.

In general the methods of assessing cost and health effects are reasonable and conform to NICE's methodological guidance and the NICE scope.

4.2.1 Modelling approach / Model structure

The company developed a Markov model to assess the cost and health effects of elosulfase alfa against standard of care for patients with MPS IVA, based on the evidence available in MPS IVA and from other closely-related diseases such as MPS VI. The model comprises six main health states: asymptomatic, no wheelchair use; some wheelchair use; wheelchair dependent; paraplegic; and end stage. Death was the remaining state, which was an absorbing state. The company states that UK based clinicians validated the model structure. The health economic model was developed in Microsoft Excel. Figure 2 presents a schematic of the company model structure.

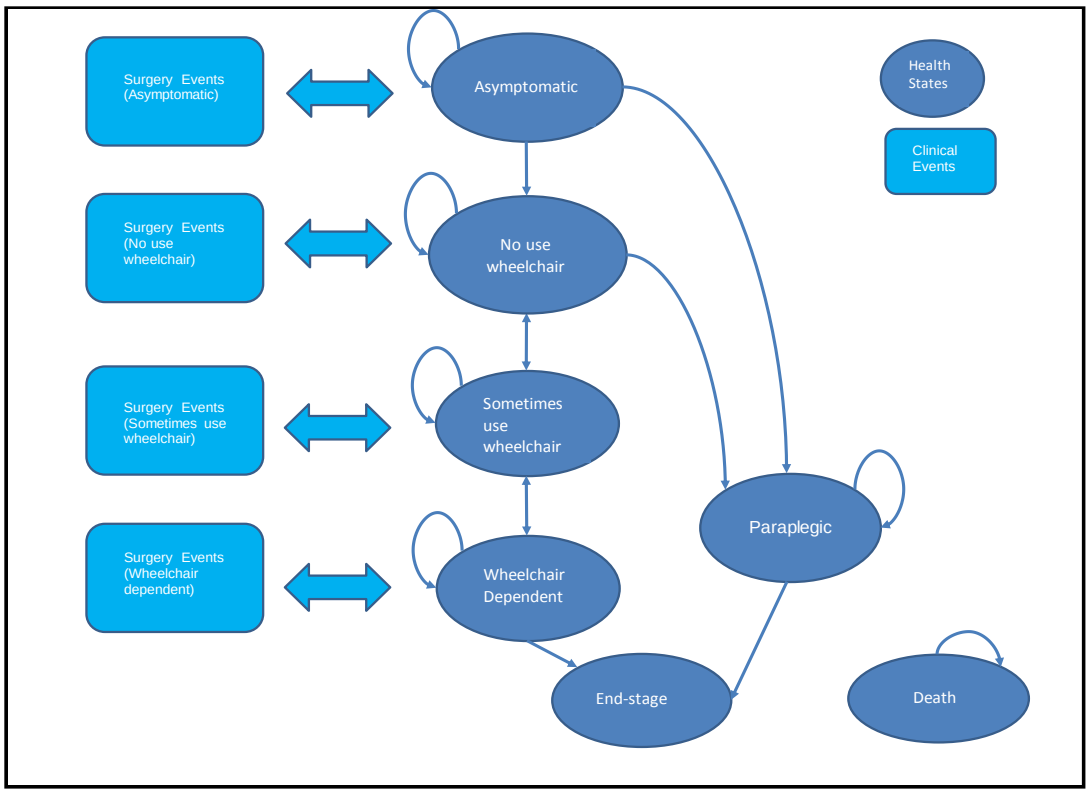


Figure 2: A schematic of the company model structure (copy of Figure 33, CS p. 162)

Disease progression in the model was accounted through four outcome measures: time to symptom development (applicable in patients in "asymptomatic" health state only); change in use of wheelchair (applicable in patients in wheelchair health states in the first cycle only); 6MWT and FVC. It was assumed that patients would develop symptoms by the age of 3 years and would progress through the first cycle based on change in wheelchair use. Progression from the second cycle onwards was based on change in 6MWT for patients in "no wheelchair" and "sometimes use wheelchair" health states, whereas for those in the "wheelchair dependent" and "paraplegic" health states disease progression was related to change in FVC.

A lifetime horizon with a cycle length of one year was used in the model. Although a half cycle correction was not stated in the CS as being applied, nonetheless this was incorporated in the economic model. The base case model incorporated a discount rate of 1.5% for both costs and QALYs. The company acknowledged that the discount rate in the NICE reference case is 3.5%. However, NICE recommends that a discount rate of 1.5% can be used for costs and QALYs in treatments where patients would otherwise not survive, patients suffer from severely impaired

life conditions or when the condition is sustained for over 30 years (NICE methods for technology appraisal, section 6.2.19[23]).

The ERG experts considered that it was reasonable to use evidence from MPS VI patients to inform the model structure due to similarities in the conditions such as skeletal dysplasia, lung involvement, cardiac involvement, and cervical spinal cord compression.

The primary source for clinical evidence was drawn from clinical and natural history studies of MPS IVA.[9;10;15] However, due to gaps in evidence, expert opinion was also used extensively to inform the model input parameters. A list of assumptions incorporated in the model was presented in CS Table D2 (p. 64), most of which were based on expert opinions. These are re-stated below in Table 29.

Table 29: List of assumptions incorporated in the Company Submission (reproduced from CS Table D2, p. 164)

1. Patients treated with elosulfase alfa would have a 5 year delay in transition from the 'asymptomatic' state to the 'no use wheelchair' health state due to delay in development of non-reversible complications and arrested disease progression
2. Improved clinical outcomes translates into greater HRQoL in treated patients versus untreated patients for each health state
3. Caregivers in each health state would suffer from a significant disutility for caring for a patient requiring significant care.
4. Caregiver costs are considered for each health state as supporting the care of patients
5. 0.1L annual decline in FVC for untreated patients in wheelchair dependent health state due to deteriorating pulmonary function
6. 2-year duration in end-stage health state for all patients
7. Delay in orthopaedic surgery in patients treated with elosulfase alfa versus untreated patients
8. Utility decrement during recovery period following surgery
9. Elosulfase alfa-treated patients would have quicker recovery rates from surgery versus untreated patients
10. 7.1m annual decline in the 6MWT for untreated patients who are not wheelchair dependent, i.e. in the asymptomatic, no wheelchair use and some wheelchair use health states
11. Slowed rate of progression of disease in multi-domain and single-domain responders
12. Increasing dependency on wheelchairs over two years in an untreated population with progressing disease.
13. Reduced dependency of a wheelchair following the first 72 weeks of elosulfase alfa treatment.
14. Mortality relative risk for untreated patients versus treated patients.

The ERG considers most of the structural assumptions made by the company as reasonable, with a few exceptions. One of the assumptions was a delay of 5 years in transition from asymptomatic health state to no use wheelchair state for patients treated with elosulfase alfa.

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 4.3.

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 4.3.

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 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

health state. However, as there are a relatively small number of patients who start in this health state, it is not likely to have a large effect on model results.

The modelled patient group reflects the licenced indication for elosulfase alfa, which is for treating MPS IVA in patients of all ages. The CS states that the MOR-001 natural history population is representative of the worldwide prevalent population and reflects all MPS IVA patients eligible to receive elosulfase alfa in accordance with its licensed indication. However, in the company's response to a clarification question from the ERG, the characteristics of the MPS IVA English population, based on AIC data from the MPS Society, show some differences from the modelled patient group. Specifically, the English population has a [redacted] mean age and [redacted] advanced disease based on wheelchair status. The company suggests that due to increased awareness of the disease and improved diagnostic procedures over time the composition of the English population would resemble that of the modelled cohort. The ERG notes that if the proportion of patients in each of the wheelchair states in the model is based on the English population rather than the MOR-001 population, there would be a slight decrease in costs and fewer QALYs gained.

The CS states that subgroup analysis was not considered appropriate given the severity and heterogeneity of the condition. As noted in section 2.3, the submission 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. The NICE scope did not specify inclusion of subgroups and the ERG is not aware of any important subgroups that should have been considered.

In summary, the patient population included in the economic evaluation, from the information available, appears to match the scope of the evaluation and the licensed indication, and reflects the population who would receive elosulfase alfa in practice.

4.2.3 Interventions and comparators

The intervention assessed is elosulfase alfa at a dose of 2mg/kg/week given by intravenous infusion. The comparator included in the economic evaluation is established clinical management without elosulfase alfa (current standard of care), as specified in the NICE scope. The current standard of care is reported to be treatment of symptoms and complications of MPS IVA with orthopaedic surgery, pain management, and treatment of infections (CS section

12.1.2). The ERG clinical experts agreed with the definition of standard care but, as reported in section 2.2, they noted that other interventions, e.g. physiotherapy, chest physiotherapy and occupational therapy are used in practice.

The CS mentions that the placebo arm of the MOR-004 trial involved enhanced care and so was not representative of the usual standard of care (CS p. 137). Furthermore, the placebo arm lasted only 24 weeks and was considered of short duration. In view of this the CS considers that the most relevant comparative arm in terms of standard clinical practice without elosulfase alfa would be the longitudinal analysis of the MOR-001 natural history study. These data were reanalysed to focus on a population that matched the MOR-004 inclusion criteria to provide a relevant cohort for comparison (CS p. 126). Further detail on this re-analysis is not provided in the CS.

4.2.4 Clinical Effectiveness

The clinical effectiveness parameters used in the model are for disease progression, surgery and mortality.

Transition probabilities

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). The transition probabilities for disease progression are shown in CS Table D15 (p. 179).

The model assumes there is a delay in the development of musculoskeletal complications by 5 years (CS p. 176) for asymptomatic patients treated with elosulfase alfa compared to those receiving standard treatment only. The CS states that this is informed by clinical opinion, based upon delay in development of symptoms seen in asymptomatic MPS I, II and VI patients initiated on ERT. The CS has included sensitivity analyses around the time delay in developing musculoskeletal complication (CS Table D32 p. 206). The ERG notes that the model results are not sensitive to changes in this parameter due to the small numbers of patients that start in the asymptomatic health state.

The first cycle in the model uses wheelchair progression data from MPS IVA patients in MOR-005 treated with elosulfase alfa and patients in MOR-001 for patients receiving standard treatment only. These data are shown in CS Table D5 (p. 168). The ERG notes that the MOR-

005 data is for 72 weeks and is used in the model for the 2-year cycle length without adjustment, and also that these data are not from an RCT which makes comparison between the treatments more uncertain.

In subsequent cycles, transition probabilities are based upon decline in 6MWT and FVC. Mean 6MWT and FVC scores for each health state and the mean score at which patients progress to the next health state are from MOR-001 study (CS Table D3 and Figure 34, p. 166). The average annual loss in 6MWT was 7 metres for patients in the no wheelchair and sometimes wheelchair health states based upon the MOR-001 study. The average annual loss in FVC was 0.1 litre in the 'always wheelchair' health state. These data were used to calculate the average time spent in each health state and thus the transition probabilities. The ERG notes that the reported transition probabilities differ from the modelled transition probabilities (CS Table D15, p. 179 elosulfase alfa treated patients). The company clarified that the transition probabilities used in the model were correct, rather than those reported in the CS.

Patients treated with elosulfase alfa differed in their disease progression according to whether they were a multi-domain responder or single-domain responder. Multi-domain responders are responders who see an improvement in both endurance and pulmonary function during the MOR-005 study, whilst single-domain responders are those who see an improvement in either endurance or pulmonary function. In the MOR-005 study, [redacted] of patients saw a significant response across multiple domains and [redacted] showed a response to a single-domain (see section 3.3 for fuller review). The company assumed that the single responders had a slowing of progression estimated to be 50% of the natural rate of decline. Patients with multi-domain response were assumed to have a stabilisation of the disease, i.e. patients do not progress to more severe health states.

The mean time spent in each health state, used to calculate the transition probabilities is shown in Table 30.

Table 30: Mean time spent in each health state (used to calculate model transition probability)

	Average time spent in health state, years		
Health state	**Natural history**	**Elosulfase alfa single-domain responders**	**Elosulfase alfa multi-domain responders**
Asymptomatic health state	3.0	8.0	8.0
No use wheelchair state	11.7	23.4	10000
Sometimes use wheelchair state	19.1	38.3	10000
Wheelchair dependent state	7.0	14.0	10000
Wheelchair dependent paraplegic	7.0	14.0	10000
End-stage health state	2	2	2

The ERG has concerns over the assumptions used to model disease progression. The MOR-005 study results for single and multi-domain responders are shown in CS Table C19 (p. 106). Single-domain responders are based upon only [redacted] patients and for these patients there was [redacted] in FVC and [redacted] of 6MWT of [redacted] at week 72 compared to baseline. Considering that patients on placebo in the MOR-004 study had an improvement in the 6MWT of about 15 metres from baseline at 24 weeks, the ERG considers there has been no improvement in 6MWT for single-domain responders. The ERG notes that the only RCT evidence presented for elosulfase alfa compared to standard care is for the 24 week MOR-004 study. Whilst an improvement in 6MWT was seen in MOR-005, there is no evidence that treatment will limit disease progression. The effect of this assumption is that the difference between 6MWT in the elosulfase alfa and standard care groups continues to increase each year. The ERG considers a more plausible effect to be that the treatment effect continues over time but does not increase, i.e. the mean 6MWT is 22.5 metres higher in the elosulfase alfa group than in the standard care group. Figure 3 below shows the 6MWT during patient lifetime for the modelled assumptions and the ERG's suggested alternative assumption. The ERG explores the effect of changing these assumptions in the ERG analyses section 4.3.

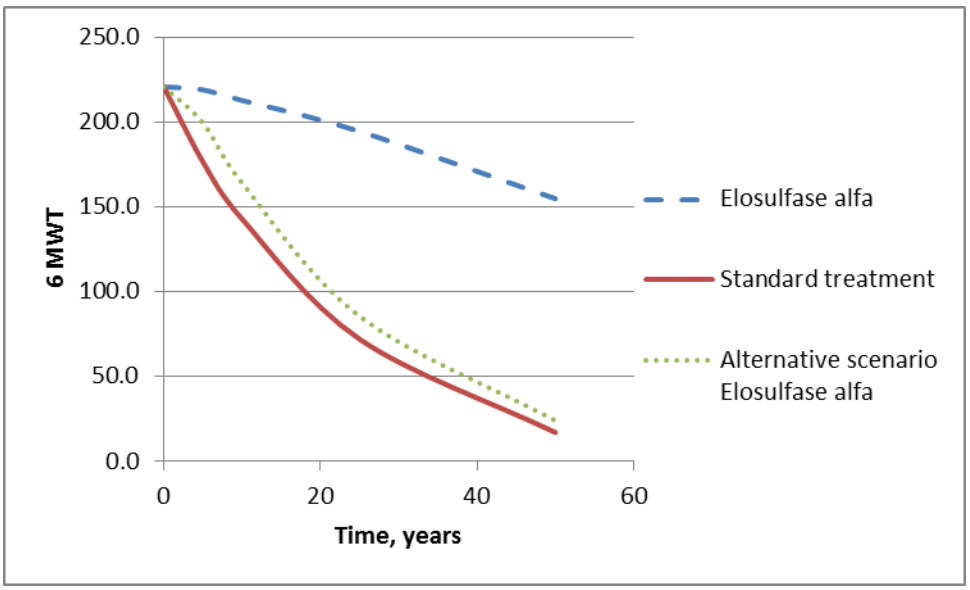


Figure 3: Mean 6MWT in the model for alternative assumptions

Mortality

Mortality is implemented as a relative risk compared to the normal population for the treated and untreated groups (CS p. 171). The relative risk of standard care patients was assumed to be 3.03 greater than of elosulfase alfa treated patients. This is based upon the assumption that the treatment with elosulfase alfa would lead to the same long-term survival benefit to that observed with galsulfase in the treatment of MPS VI.[24] The CS states that this assumption is supported by evidence indicating ERT used for MPS conditions is associated with similar mechanisms of improvement in pulmonary function as elosulfase alfa. The CS states that results of a 10 year study of MPS VI have shown that the rate of mortality for galsulfase treated patients was 3.03 times less than that of untreated patients (i.e. 16.5% versus 50%). The model assumes that patients treated with elosulfase alfa would have the same mortality risk as that of the general population. The CS includes a sensitivity analysis with an alternative approach to mortality, whereby a relative risk ratio compared to background mortality is applied based on the percent decrement in FVC compared to the general population.

The ERG has concerns about the assumptions used to estimate mortality. As discussed earlier, the model assumes that elosulfase alfa delays disease progression which results in mortality benefit. In the CS base case results, CS Table D24 (p. 200) shows that 2.68% of modelled patients treated with elosulfase alfa have died after 10 years compared to 16.66% of standard care patients, i.e. 6.22 times higher. The ERG therefore believes the benefits for mortality have been overstated and have already been included through the transition probabilities used in the

model and no additional mortality benefit should be included, i.e. without the additional mortality benefit there is still lower mortality in the elosulfase alfa patients with a relative risk of more than 3.03 over 10 years. The ERG explores the effect of changing these assumptions in the ERG analyses section 4.3.

Surgery

In each health state a proportion of patients undergo different types of surgery to alleviate their symptoms and preserve their functional status. These are treated as clinical events and do not affect the health state of the patient. For each surgical event, patients have a risk of complications (CS Tables D11 and D12, p. 174-5), including a risk of death (CS Table D16 p.184). After surgery patients enter a recovery period during which they have a reduced QoL. The proportion of each type of surgery per health state, rates of surgical complications, the duration and utility decrements of the recovery period are based on clinical opinion from UK experts obtained via the Delphi process. A list of the assumptions around surgeries is listed in the CS (p. 182).

The economic model does not include any AEs for treatment with elosulfase alfa. The CS states that AEs were not included in the analysis as the only drug-related AEs experienced were infusion reactions, which are not considered to have a substantial impact on HRQoL. The ERG discussed the AEs in section 3.3.

In general, the ERG considers that the company's approach to estimate clinical effectiveness and other transition probabilities contains assumptions which are not consistent with the limited clinical evidence presented, and are likely to overestimate the benefit of treatment with elosulfase alfa.

4.2.5 Patient outcomes

Utility estimates are assigned to each of the main model health states, decreasing according to the progressive nature of the disease (0.959 for the asymptomatic state; 0.846 for the no wheelchair use state; 0.582 for the sometimes use wheelchair state; 0.057 for the wheelchair dependent state; 0.057 for the paraplegic state; and 0.024 for the end-stage state) (CS Table C29 p.151). Utility increments are applied to elosulfase alfa-treated patients in four of the six health states (no wheelchair use; sometimes use wheelchair; wheelchair dependent; paraplegic) (see below). Utility loss associated with AEs is not included. The submission states that AEs are

mostly infusion-related and are managed by slowing infusions and premedication. They are therefore not considered to have a substantially relevant impact on HRQoL. The ERG clinical experts note that SAEs may be managed with immunosuppressants.

In terms of source data for the health states, for the asymptomatic health state the utility estimate is based on standard UK population EQ-5D scores for children aged 0 - 9 years. The ERG clinical experts agreed that this reflected the HRQoL of patients prior to developing symptoms. The burden of illness study by Hendriksz and colleagues (2014)[8] provides adult patient utility estimates for four of the model health states (no wheelchair use; sometimes use wheelchair; wheelchair dependent; end-stage). This was the only relevant study identified by the company's systematic review of HRQoL (CS Section 10.1.5). The ERG considers that the methods to conduct the systematic review are reasonable (see Section 3.1.1), though there is no critical appraisal of the included study. The ERG is not aware of any alternative relevant studies. The study was conducted with ERT naive patients (n=27 adults aged ≥ 18 years, and 36 children aged 7-17 years) from South America, Germany, Spain, Turkey and a minority from the UK (n=1), who completed the EQ-5D-5L questionnaire. The study reports both adult and child utilities, but only the adult utilities are used in the model with no reason stated for this. The ERG notes that the child utilities show a different pattern to the adult utilities: 0.534, 0.664, 0.180 for the no wheelchair use, sometimes use wheelchair, and wheelchair dependent health states, respectively. Of note is that there was a smaller number of adult than child patients in the no wheelchair use group in the study (n=4 versus n=18, respectively), and a higher number of adult than child patients in the always use wheelchair state (n=9 versus n=2, respectively), which may have influenced the discrepant findings. Furthermore, the ERG notes that the child utilities would only apply to the asymptomatic, no wheelchair use and sometimes use a wheelchair health states as the starting ages are 0, 12 and 17 years, respectively in those states (see Section 4.2.2).

The burden of illness study[8] did not provide a utility estimate for the paraplegic health state. A Delphi exercise was conducted with seven UK clinical experts in treating MPS IVA (5 of whom responded) (CS Section 10.1.10). The experts initially did not agree with the suggestion that the utility for this health state would be the same as the utility for the wheelchair dependent health state (0.057). In a subsequent round the majority of experts agreed that HRQoL would be worse for paraplegic patients. However, following an expert panel meeting the CS states that paraplegic patients would have worse HRQoL at first, but overall would be better than patients

in the wheelchair dependent state. Given this statement, it is unclear why the utility value adopted for the two health states in the model is the same. The ERG clinical experts note that some patients can become paraplegic through disease progression (the CS assumes that paraplegia only occurs through surgical complication). It is therefore possible that a proportion of patients in the paraplegic health state could have worse HRQoL than the wheelchair dependent state (due to general disease progression, as opposed to better HRQoL experienced by people becoming paraplegic through surgical complications from an earlier, less progressed, health state). The experts participating in the Delphi exercise are reported to have agreed with the other health state utility values from the burden of illness study.[8]

The ERG notes that there is a marked and statistically significant decline in utility between the sometimes use a wheelchair health state and the wheelchair dependent health state from 0.582 to 0.057. There were mixed views among the ERG's clinical experts regarding whether this is realistic. The CS does not comment on the factors influencing this decline, however the burden of illness study publication, from which the utilities were derived, notes that the negative impact of wheelchair use on HRQoL was influenced by worse scores for the EQ-5D domains of mobility, self-care and usual activities.[8] There was a similar marked increase in the average number of caregiving hours for adult patients if a wheelchair was used only when needed (3.9 hours per day) to when the wheelchair was always used (13.8 hours). The publication also notes that being unemployed was statistically significantly associated with a lower HRQoL than being employed and that adult patients who always had to use their wheelchair had a high chance of being unemployed.[8] For context, the ERG identified a study of EQ-5D utility data collected in UK patients with MS, which also showed a marked utility decline (albeit of smaller magnitude) according to reduced mobility: mean utility score of 0.643 for patients able to walk up to 250 metres unaided, 0.369 for patients who could walk indoors with assistance, and 0.015 for wheelchair dependent patients.[25]

Utility increments

Utility increments associated with elosulfase alfa treatment are based on changes in the 6MWT (no wheelchair use and sometimes wheel chair use states) and lung function (FVC) (wheelchair dependent and paraplegic health states) from the MOR-005 extension study (week 72 interim analysis). The CS states that utilities were derived by mapping between the MOR-005 extension study, the longitudinal natural history (MOR-001) study and the burden of illness study.[8] Little

further information is provided in the submission on this process. The methods and assumptions for estimating treatment-associated utility increments appear to be:

- For every 10 metres increase in 6MWT there was a 0.02 increase in QoL (no wheelchair use and sometimes wheelchair use states). This assumption was based on an AIC publication by Lampe and colleagues (2014)[26], sponsored by the company, of a sample of 25 German MPS IVA patients from the burden of illness study[8]. The study conducted a regression analysis to assess the correlation between endurance and pulmonary function taken from the MOR-001 natural history study[15] Mainz clinical database, with EQ-5D-5L utility scores from the burden of illness study.[8] The study showed for every 40 metre improvement in 6MWT the HRQoL utility value improved by 0.08. Of note is that correlations were strong for all patients and for the subgroup of adult patients, but not for the subgroup of child patients. This assumption was then applied to the week 72 6MWT results of the MOR-005 study and the MOR-001 natural history annual decrease. The model used an improvement of 55.7m, leading to a utility increment of 0.11 in the wheelchair use and sometimes wheelchair use health states.
- For every 1 litre improvement in FVC there was a 0.2 increase in QoL (wheelchair dependent and paraplegic health states). The source of this assumption is not stated. However, the ERG notes that the AIC publication by Lampe and colleagues (2014)[26] reports a moderate but statistically significant correlation between FVC and the EQ-5D-5L (though it does not quantify the improvement in FVC and utility, therefore it is not clear how the 0.2 increase in QoL is derived). This assumption was then applied to the results of the MOR-005 extension study. The model used an improvement of 0.0885 litres, leading to an improvement of 0.017 for the wheelchair dependent and paraplegic health states.

The ERG has concerns regarding the validity of utility increment in the company's economic model. The ERG calculated the mean utility at different time points of the model, based on the proportion of patients in each health state, both for the company's base case and an analysis without the utility increment. The mean utility score for the patients treated with elosulfase alfa and with standard treatment are shown in Table 31 at 0, 2 and 5 years using the base case assumption of a utility increment and without a utility increment. The ERG notes that at year 0 the mean utility is 0.1 greater for the elosulfase alfa patients than for those with standard treatment for the base case assumption including a utility increment. At 2 years, for the scenario without an increment there is a difference in utility between the elosulfase alfa and standard

treatment groups of 0.08, i.e. similar to that estimated by the CS for the MOR-005 extension study. At 2 years, for the baseline scenario with a utility increment there is a difference in utility between the elosulfase alfa and standard treatment groups of 0.18, i.e. an overestimate of the utility gain estimated by the CS for the MOR-005 extension study. The ERG therefore concludes that the utility increment is double counting the utility benefit from elosulfase alfa and should be removed. This is explored in the additional analyses conducted by the ERG, presented in section 4.3.

Table 31: Mean utility for elosulfase alfa and standard treatment patients with and without utility increment in the Company model

	Mean utility with utility increment (base case)			Mean utility without utility increment		
Years	Elosulfase alfa	Standard treatment	Difference	Elosulfase alfa	Standard treatment	Difference
0	0.76	0.66	0.1	0.66	0.66	0
2	0.78	0.60	0.18	0.68	0.60	0.08
5	0.77	0.53	0.24	0.67	0.53	0.14

The MOR-004 and MOR-005 extension study used the MPS HAQ, which is reported to be sensitive for the caregiver and mobility domains. However, results of the MPS HAQ do not appear to be used in the calculation of utility estimates. The ERG notes that the EQ-5D-5L preference valuation set used in the burden of illness study[8] to generate the health state utilities is not explicitly stated. As studies to assess valuation sets are in progress it is possible that one of the interim 'crosswalk' sets for the 5L was used.

A utility benefit of 0.02 was assumed for the 90% of patients receiving home infusions, to reflect the additional convenience, reduced stress and discomfort to patients and their caregivers. This assumption is based on evidence from other lysosomal storage disorders, which have shown improvements in quality of life once patients are switched to home care therapy. Removal of this benefit in a scenario analysis had little impact on the incremental costs and QALYs (CS section 12.5.14).

Caregiver utilities

The economic evaluation also assesses the HRQoL of carers. Carer disutilities for each health state were derived by estimating the number of hours caregiving per day from the burden of illness study[8] (stratified by frequency of wheelchair use), and then matching to the corresponding multiple sclerosis Extended Disability Status Scale EDSS state to give a proxy

utility value (CS Table C30 and Table C31, p.151-2) taken from a study by Gani and colleagues,[27] which was used in the NICE technology appraisal for fingolimod for the treatment of relapsing-remitting MS in adults (NICE TA254[28]). The submission also cites an observational study of caregivers of people with MS in the UK who completed the EQ-5D and the Patient Determined Disease Steps questionnaire as a measure of MS severity (Acaster and colleagues[29]), that can be used as an alternative scenario to the base case (CS Table C32 p.153). Elsewhere in the CS it states that a scenario analysis is conducted to explore the removal of caregiver disutility based on Acaster and colleagues.[29] The ERG notes that all of the caregiver disutility estimates in the model are based, by default, on the study by Gani and colleagues.[27] Reference to results based on disutilities by Acaster and colleagues[29] in the submission appear to be an error. (NB. the model does have a setting which does use the Acaster data, but results are not given in the submission. The Acaster utility estimates produce slightly fewer incremental QALYs than the Gani utility estimates).

CS Table D14 (p. 178) reports utility decrements associated with the recovery period following 10 surgical procedures. Estimates are based on UK expert clinical opinion from the Delphi exercise mentioned previously. For musculoskeletal surgery (e.g. cervical fusion surgery, spinal decompression etc.) a utility decrement of 0.250 is applied and elosulfase alpha-treated patients are assumed to have a 2 months shorter recovery period. Other, types of surgery (e.g. tonsillectomy, corneal replacement) is associated with a smaller utility decrement (0.005) but a 50% lower recovery period for elosulfase alpha.

In summary, the ERG considers that the company's assessment of patient outcomes is generally reasonable though with some uncertainties. The main potential limitation is the possible double counting of the treatment-associated utility increment. The ERG has conducted a scenario analysis to explore this in Section 4.3.

4.2.6 Resource use

Resource use reported in the CS includes those associated with drug costs, including drug administration), health state costs, surgery costs, and caregiver costs.

Drug use in the model is based upon a recommended dosing of weekly elosulfase alfa of 2mg/kg of patient body weight. Elosulfase alfa is administered by infusion made up of 5ml vials, each containing 5 mg elosulfase alfa. Any remaining drug after infusion is assumed to discarded

and for the purposes of the model, the number of vials to be administered is rounded up to the nearest whole number. The company assumed that 90% of patients have home infusions of ERT with or without the supervision of a nurse, following an initial 3-month period of receiving the infusion in a hospital (outpatient setting), based upon evidence from the Gaucher's Disease Association.[30]

Health state costs were based upon the consumption of health care resources, such as GP visits, hospital attendance and ventilation. The resources used for each health state were sourced from an expert panel of physicians and are shown in CS Table D21 (p. 193). In addition, patients received additional care from a professional carer and by family members. The CS assumed that 50% of caregiver hours will be covered by professional carers and 50% by family members. The numbers of hours of caregiving per day varies by health state and is shown in CS Table D4 (p. 167); these values were taken from the burden of illness study.[8] This study evaluated the global burden among primary caregivers of patients with MPS IVA and consisted of 56 caregivers from five different countries. The survey was mostly for children (n=37), although the results used in the model were from adults (n=19). The CS does not provide a rationale for why values were taken from adults, rather than children. The ERG considers that it is reasonable to choose the adult values as patients spend most of the modelled duration as adults.

Overall, the estimates used for the choice of resources used in the modelling appear appropriate and relevant to the patients with MPS IVA.

4.2.7 Costs

Drug acquisition costs applied in the model are £750 per 5ml vial (CS Table D19 p.192). The cost of elosulfase alfa was discounted by 20% for patients who receive home therapy due to the VAT waiver for home infusion drugs. The ERG believes this is an incorrect approach to costing. According to the NICE methods guide, VAT should be excluded from all economic evaluations (5.5.10), therefore there would be no difference between the drug cost between home and hospital care. The ERG explores removing this price reduction in a scenario analysis in Section 4.3. The drug administration cost is taken from the outpatient cost for vascular access from Payment by Results Tariff (2013-14).[31] The ERG notes that the patient weight differs per health state but does not vary over time. This mainly affects patients in the asymptomatic health state

who start at 12kg, however there are a relatively small number of patients who start in this health state and so it is not likely to have a large effect on model results.

Unit costs of resources and surgeries were obtained from NHS reference costs 2011-12;[32] literature sources and PSSRU unit costs of health and social care 2012.[33] Health state costs were calculated by multiplying the resource use estimates reported in CS Table D21 (p. 193) by the unit costs shown in CS Table D22 (p. 194).The ERG notes that the unit costs were different in the CS to those used in the model. The company clarified that the costs had not been updated in the model with the latest version of the NHS reference costs. The company provided an updated analysis which showed the impact of making this change is negligible.

Caregiver costs were £24 per hour, taken from Table 11.6 in PSSRU 2013.[33]

Overall, the ERG notes that the approach to valuing the resource use is consistent with the NICE reference case, except for in relation to a reduction in drug cost for home infusion. Values have been taken from standard sources, are indexed to the current price year and estimates have been appropriately reported.

4.2.8 Consistency/ Model validation

Internal consistency

The company did not provide any details on quality checks performed on the health economic model to validate its functionality. The ERG conducted a range of random checks of the model for some of the key calculations in the model. The 'wiring' of the model appear to be mostly accurate, with minor errors in the estimation of probabilistic values for a few parameters, details which are discussed in section 4.2.9. However, a comprehensive check of all the cells in the model was not performed. On cross-checking the results reported in the CS against the Excel model, the ERG found a minor typing error of the total costs in the text of CS p. 203 (reported as [redacted] instead of [redacted]). A list of verification checks was conducted by the ERG to examine if varying input parameter values would generate intuitive model results. Overall, the ERG views the company model to be well presented. The model was user friendly and adopted a reasonable approach in modelling a rare condition such as MPS IVA.

External consistency

The company did not conduct data validation of the economic model against existing literature due to lack of long term studies on the natural history of the condition. In addition there was also a dearth of studies analysing the impact of ERT on disease progression. The company, however, validated the economic model by comparing the life expectancy (life years gained) and causes of death in the natural history model against a recently published UK mortality study for MPS IVA patients by Lavery and Hendriksz[34]. The company states these to be validated by UK clinical experts. The ERG found the findings in the model concurred with those of the published evidence, but could not validate the model results against the findings in the clinical trial as it incorporated a yearly cycle without adjusting for the 72 weeks MOR-005 trial data.

4.2.9 Assessment of Uncertainty

One-way sensitivity analyses

The company conducted a series of deterministic univariate sensitivity analyses on the base case model results (presented in CS Table D23, p. 197). Model parameters included in the analyses were discount rates for costs and QALYs, average body weight per health state, annual decline in the 6MWT, annual decline in FVC, utilities, costs, delay in becoming asymptomatic due to elosulfase alfa treatment, delay in surgery and utility benefit associated with home care. The interval range applied for the parameters varied. For instance, a lower and upper bound of 95% confidence intervals was applied to average weight per health state except for those in the asymptomatic state, where a range of ±10% was applied. For the annual decline in 6MWT and FVC, a range of ±25% was used. All costs and utilities were varied by ±10%. While a range of ±10% was applied for the delay in surgery, the lower and upper bound of 3 and 10 years respectively were applied for delay in becoming symptomatic with treatment. Discount rates for costs and QALYs were varied between 0% and 6%. Finally, a lower and upper limit of 0 and 0.05 was assumed for utility benefit associated with home care. These values were mostly derived from assumptions based on expert opinions.

The results of the sensitivity analyses were presented diagrammatically in a tornado diagram (CS Table D32 and Figure 35, p. 206-7). The CS stated that model results were most sensitive to discount rates for costs and QALYs. Other parameters including annual decline in the 6MWT values, surgery costs, utility values and average body weight per health states had very limited impact on the base case results. Of note is that the company reported the impact on QALYs for

change in parameter values in CS Table D32 (p. 206-7), but did not report the impact on costs. The ERG explored this and observed that the impact on costs from the deterministic analyses was similar to that reported for the impact on QALYs in terms of which parameters have the most impact on the model results.

The ERG observed slight discrepancies in reporting of lower and upper intervals in the CS report and the model for average body weight in asymptomatic state; annual decline in 6MWT for patients in no wheelchair use and sometimes wheelchair use states; annual decline in FVC for wheelchair dependent and paraplegic health states. Further, a lower and upper range of 0.88 to 0.97 was assigned for ranges for the utility associated with the asymptomatic health state, but in the base case there was a mean value of 1.00. In addition, the tornado diagram obtained in the model after running the one-way sensitivity analysis by the ERG differed slightly from the one reported in CS Figure 35 (p. 207).

The ERG has reservations about the interval ranges used in the sensitivity analyses for costs and utilities. Therefore, the range was broadened by ±25% to assess the impact on base case results. The results did not differ considerably and similar parameters were found to influence the base case values as observed with an interval range of ±10%.

Scenario analysis

The company conducted a number of scenario analyses to assess the impact of key structural assumptions in the base case model (presented in CS Table D23.2 and p. 198). These analyses were conducted to account for changes in assumptions such as assuming all patients started treatment from birth (i.e. in the asymptomatic health state); inclusion of societal perspective to include work productivity loss; removal of caregiver costs and utilities; estimating mortality based on modelling of predicted percentage FVC versus generalised mortality; and inclusion of additional homecare utility benefit of 0.002 QALYs. The results of the scenario analyses were presented in CS Tables D33 - D46 (p. 208-11).

On re-running the scenario analyses, the ERG was able to replicate most of the results as reported in the CS. However, there were some discrepancies. The undiscounted total costs reported in the CS differed by £4 from the Excel model for the scenario where caregiver disutility is removed. The undiscounted and discounted total costs for elosulfase alfa varied by approximately [redacted] and [redacted] respectively when mortality was assumed to be related to

changes in FVC. For the scenario of additional utility benefit for homecare, the reported undiscounted and discounted QALYs for elosulfase alfa varied by approximately 7 and 5 QALYs respectively. Finally, in the multi-way scenario analysis with a 2-year delay in symptom development due to elosulfase alfa treatment of asymptomatic patients with 80% progression rate of single-domain responders compared to untreated patients, the ERG found a discrepancy of approximately [redacted] in the incremental costs from the value reported in the CS. The scenario where all patients start their treatment with elosulfase alfa from birth leads to a reduction in incremental costs and incremental life years by [redacted] and 0.8 respectively and an increase in incremental QALYs by 0.05, compared to the base case results.

Despite the inconsistencies listed above, the scenario analyses appeared to be reasonable. Overall, the ERG considers that additional scenarios could be explored for some of the structural assumptions, which are discussed in detail in Section 4.3.

Probabilistic sensitivity analysis (PSA)

The probabilistic sensitivity analysis was conducted for 1000 simulations with a run-time of about a minute. This can be run by clicking the button “Run Probabilistic Sensitivity Analysis” in the ‘PSA’ worksheet in the model. The parameters included in the PSA were reported in the CS (Table D23.3; p. 198). No justification was provided for the assigned distributions to the input parameters. Although some of the assigned distributions were reasonable, the ERG felt that others were inappropriate. For instance, the company assigned a normal distribution for both costs and utilities. The CS stated that utilities were assigned a beta distribution but in the model, the normal distribution was assigned. The ERG considers that it would have been appropriate to assign gamma distribution for costs and beta distribution for utilities, as per usual modelling practice. The ERG conducted a probabilistic sensitivity analysis by assigning these distributions to costs and utilities and the results obtained provided closer estimates to the mean deterministic incremental costs, QALYs and life years to the base case results, compared to the probabilistic values reported by the company. Dirichlet / Beta distributions were assigned for wheelchair shift proportions. Assigning the Dirichlet distribution was considered appropriate as the multiple outcomes (death, success and paraplegic) were mutually exclusive. For the remaining parameters such as average weight per health state, average decline in 6MWT, average decline in FVC, delay in surgery and delay in becoming symptomatic with treatment, normal distributions were assigned.....

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

PSA results obtained by the company						
	Discounted			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
No Treatment	[redacted]	9.67	27.53			
Elosulfase Alfa	[redacted]	27.02	61.19	[redacted]	17.35	33.66
Corrected PSA results obtained by the ERG						
	Discounted			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
No Treatment	[redacted]	9.71	27.75			
Elosulfase Alfa	[redacted]	27.23	61.50	[redacted]	17.52	33.75

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 the 24-week trial results to a lifetime horizon. The model assumes that patients' treatment with elosulfase alfa would lead to a stabilisation of disease, 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.

The company model assumes that treatment with elosulfase alfa provides a utility increment for patients, however, the ERG considers that this utility benefit is apparent in the model due to a slower progression of patients to more severe health states. Therefore the ERG believes that the model is double counting the utility benefit from treatment and this utility increment should be removed. In a similar manner, the ERG believes that the model is double counting the mortality benefit for elosulfase alfa.

In addition, the company model has included a reduction in drug costs for patients treated elosulfase alfa with home infusions due to a VAT waiver. However the ERG notes that NICE does not consider VAT in technology appraisals and therefore this cost reduction should be removed.

The ERG considers that these concerns largely affect the validity of the results and re-run scenario analyses making changes to these assumptions in section 4.3.

4.3 Additional work undertaken by the ERG

The ERG conducted further exploration of the issues and uncertainties raised in the review and critique of the CS economic analyses. The analyses conducted were:

i. Using a discount rate of 3.5% for both costs and QALYs
ii. No reduction in drug cost for VAT for home infusions
iii. Changes in the assumptions for treatment effect of elosulfase alfa, with respect to:
    - No benefit for single-domain responders
    - Less benefit for multi-domain responders
iv. No mortality benefit for patients with elosulfase alfa
v. No utility increment for patients treated with elosulfase alfa
vi. Using lower and upper range of 95% confidence intervals for the health state utilities
vii. Combined scenario (scenarios ii to v) with no reduction in drug cost for VAT for home infusion + no benefit for single-domain responder and less benefit for multi-domain responder + no mortality benefit + no utility benefit for patients with elosulfase alfa

i. Discount rate of 3.5% for costs and QALYs

The ERG conducted an analysis with a discount rate of 3.5% for both costs and QALYs. The results are presented in Table 33 below. The incremental costs reduced from [redacted] in the base case to [redacted] in the scenario and incremental QALYs declined from 18.18 to 10.28.

Table 33: Discount rate at 3.5% for costs and QALYs

	Total			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
Standard care	£450,538	7.67	27.96	[redacted]	10.28	34.10
Elosulfase alfa	[redacted]	17.95	62.06			

ii. No reduction in drug cost for VAT for home infusions

The ERG expressed concerns about the company assumption of reducing the cost of elosulfase alfa by 20% for patients receiving home infusion. A scenario with no reduction in drug cost was conducted. The results (presented in Table 34) show in an increase in total incremental costs by [redacted], while incremental QALYs remain similar, indicating that this assumption favours elosulfase alfa.

Table 34: No reduction in drug cost for VAT for home infusions

	Total			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
Standard care	£618,812	9.75	27.96	[redacted]	18.18	34.10
Elosulfase alfa	[redacted]	27.93	62.06			

iii. Changes to assumptions in the treatment effect of elosulfase alfa, relating to disease progression

- **No benefit for single-domain responders**

The ERG explored the impact of incorporating no benefit for the rate of disease progression for single-domain responders in the elosulfase alfa treatment group for subsequent time periods after 2 years. This resulted in lower total costs ([redacted] vs [redacted] in the base case); lower QALYs (24.49 vs 27.93 in the base case) and fewer life years (56.79 vs 62.06 in the base case) for the patients treated with elosulfase alfa, as shown in Table 35.

Table 35: No benefit for single-domain responders

	Total			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
Standard care	£618,812	9.75	27.96	[redacted]	14.73	28.84
Elosulfase alfa	[redacted]	24.49	56.79			

- **Less benefit for multi-domain responders**

In the base case analysis, the company assumed that multi-domain responders would have a stabilisation of disease from the treatment. The ERG conducted two scenarios where multi-domain responders with elosulfase alfa treatment have less benefit with regard to disease progression, with a 50% reduction in the rate of decline and a natural rate of decline for subsequent years after 2 years, compared to the patients receiving standard care (Table 36). These scenarios have significant impact on the model results with a decline in incremental costs by [redacted] and [redacted]; QALYs by 8.14 and 12.93 and life years by 14.94 and 26.42 respectively, compared to the base case results.

Table 36: Less benefit for multi-domain responders (50% rate of decline for subsequent time period after 2 years)

	Total			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
Standard care	£618,812	9.75	27.96	--	--	--
Elosulfase alfa (50% rate of decline)	[redacted]	19.79	47.12	[redacted]	10.03	19.16
Elosulfase alfa (natural rate of decline)	[redacted]	15.00	35.64	[redacted]	5.24	7.68

iv. No additional mortality benefit for patients treated with elosulfase alfa

The ERG had reservations about the company's assumption of an additional mortality risk benefit for patients treated with elosulfase alfa. Therefore, a scenario analysis was conducted where no such benefit was assumed in the treatment group. The results obtained (Table 37) were not substantially different from the base case results with an increase in total incremental costs of [redacted] QALYs by 0.25 and life years by 1.49. This indicates that changes in the assumptions for mortality are not a significant factor driving the results.

Table 37: No mortality benefit for patients treated with elosulfase alfa

	Total			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
Standard care	£645,038	10.00	29.45	[redacted]	17.93	32.61
Elosulfase alfa	[redacted]	27.93	62.06			

v. Utility benefits

Based on the ERG's view that the utility benefit of elosulfase alfa has been double counted (as discussed in section 4.2.5 of this report), the ERG conducted a scenario analysis with no additional utility increment for patients treated with elosulfase alfa. The results, presented in Table 38, show a decline in total QALYs for patients treated with elosulfase alfa with a decline in incremental QALYs from 18.18 QALYs in the base case to 14.22 QALYs. There were no changes in costs.

Table 38: No additional utility increment for patients treated with elosulfase alfa

	Total			Incremental		
	Costs	QALYs	Life Years	Costs	QALYs	Life Years
Standard care	£618,812	9.75	27.96	[redacted]	14.22	34.10
Elosulfase alfa	[redacted]	23.97	62.06			

vi. Using lower and upper range of 95% confidence intervals for the health state utilities

The ERG noted that the company had used arbitrary ranges for the sensitivity analyses for health state utilities. The ERG investigated the impact of using the confidence intervals for the range of values associated with health state utilities. The ERG conducted two scenarios using the lower and upper range of the 95% confidence intervals for the health state utilities (shown in Table 39). The results obtained (shown in Table 40) indicate that when lower utility values are incorporated, total QALYs in the base case decline from 9.75 and 27.93 for standard care and elosulfase alfa respectively, to 6.53 and 22.44 respectively. When the upper intervals are used total QALYs increase to 12.92 and 33.38, respectively.

Table 39: Health state utility values

	Asymptomatic	No use wheelchair	Sometimes use wheelchair	Wheelchair dependent	Paraplegic	End stage
Lower CI	0.959	0.707	0.459	-0.165	-0.165	-0.134
Upper CI	0.959	0.985	0.705	0.278	0.278	0.158

Table 40: Results of scenario with lower and upper range of utility values

Lower range of health state utility values						
	Total			**Incremental**		
	Costs	**QALYs**	**Life years**	**Costs**	**QALYs**	**Life years**
Standard care	[redacted]	6.53	27.96	[redacted]	15.91	34.10
Elosulfase alfa	[redacted]	22.44	62.06			
Upper range of health state utility values						
	Total			**Incremental**		
	Costs	**QALYs**	**Life years**	**Costs**	**QALYs**	**Life years**
Standard care	[redacted]	12.92	27.96	[redacted]	20.46	34.10
Elosulfase alfa	[redacted]	33.38	62.06			

Vii. Combined scenario with no reduction in drug cost for VAT for home infusion + no benefit for single-domain responder and less benefit for multi-domain responder + no mortality benefit + no additional utility increment for patients with elosulfase alfa

The ERG conducted a combined scenario (scenarios ii to v). The results are shown in Table 41. There is a decline in incremental costs, QALYs and life years in the combined scenario with a difference of [redacted]; 13.14 QALYs and 21.26 life years respectively for 50% reduction rate and [redacted]; 16.55 QALYs and 31.15 life years respectively for natural rate of decline for multi- domain responders, respectively. Of note is that there is a substantial reduction in QALYs and life years when multi-domain responders treated with elosulfase alfa were assumed to have a natural rate of decline.

Table 41: Combined scenario (with no reduction in drug cost; no benefit for single and less benefit multi-domain responders; no mortality benefit and no utility benefit for patients with elosulfase alfa)

	Total			**Incremental**		
	Costs	**QALYs**	**Life Years**	**Costs**	**QALYs**	**Life Years**
Standard care	£645,038	10.00	29.45	--	--	--
Elosulfase alfa (50% natural rate of decline)	[redacted]	15.04	42.29	[redacted]	5.04	12.84
Elosulfase alfa (at natural rate of decline)	[redacted]	11.63	32.4	[redacted]	1.63	2.95

4.4 Summary of uncertainties and issues

There is substantial uncertainty over the estimation of the long term treatment effect of elosulfase alfa. The clinical trial evidence presented from the MOR-004 trial for elosulfase alfa compared to placebo is for 24 weeks and there are difficulties with extrapolating these data to a patient lifetime. In particular the company assumes that the treatment leads to no further

disease progression for multi-domain responders. Given the limited trial evidence available, there is considerable uncertainty around this assumption.

The CS reports a benefit for patients treated with elosulfase alfa, in terms of a utility increment and a mortality benefit for these patients. This benefit is apparent in the model, due to the slower progression in patients treated with elosulfase alfa compared to those with standard treatment, and therefore these benefits appears to have been counted twice.

5 Cost to the NHS and PSS

The CS includes an analysis of the estimated budget impact of elosulfase alfa for NHS and PSS. The budget impact uses the data inputs described for the economic model described in section 4.2.1 of this report. The budget impact model estimates the total costs to the NHS for the period from 2016 to 2020.

The budget impact model has used the estimated prevalence and incidence rates of MPS IVA patients in England. The company estimates that there are currently 88 IVA patients in England who would be eligible for treatment in year 1, based on the number currently listed on the MPS disease registry. They assume 2.7 babies would be born with MPS IVA per year (based on an incidence of 1 in 250 000 live births and 654 717 live births in England per year).

The company assumes that from these patients, 74 of the prevalent patients would want treatment and 50 would, in fact, receive treatment in year 1. In addition, the 2.7 patients born in this year would be treated with elosulfase alfa. Thus 52.7 patients are treated in year 1. In year 2, the company assumes that all eligible patients receive treatment (77 patients) and newly born patients (2.7 patients). Thus 82.3 patients are treated in year 2. In each subsequent year, a further 2.7 patients are treated.

The estimated costs are shown in Table 42 (CS Table D47, p. 220) for the case where elosulfase alfa is funded and a second scenario where elosulfase alfa is not funded.

Table 42: Estimated budget impact for the NHS and PSS (Reproduced from CS Table D47, p. 220)

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Elosulfase alfa available scenario	£19,091,117	£30,122,021	£29,988,247	£30,519,313	£31,058,760
Elosulfase alfa not available scenario	£1,780,553	£1,833,534	£2,106,843	£2,176,248	£2,235,111
Net budget impact	£17,310,564	£28,288,486	£27,881,403	£28,343,064	£28,823,649

The CS stated that clinical experts based in the UK validated the estimated number of eligible and actual patients, along with expected uptake rate.

NICE has requested information from Consultees on the number of people with MPS IVA that would be expected to receive elosulfase alfa if it were to be recommended. The Consultees were in agreement that the number of people in the UK is around 89 patients. Two Consultees (NHS England and Save Babies Through Screening Foundation UK) estimated that 77 of these would be interested in receiving this form of treatment if it were available (based on estimates from the MPS society). The other Consultees gave their opinion on what number would take up treatment, ranging from 60 to 80 patients.

According to the MPS society website, 26 babies were born with MPS IVA in the UK between 1989 and 1999.

The ERG conducted a number of verification checks on the budget impact analysis. Although the calculations appear plausible, the estimated values reported in the CS Tables D47 and D48 (p. 220, 221) do not match the values in the model, although the differences are small.

The ERG ran the following scenario analyses to assess the net budget impact of introducing elosulfase alfa in the treatment of patients with MPS IV.

i. No reduction in drug costs for home infusions

The ERG suggests that the company have incorrectly included a cost reduction for home infusion. In this scenario, the ERG assumed that there would no reduction in drug costs for patients with home infusions of elosulfase alfa (Table 43). The net budget impact increases by around [redacted] in the first year and by around [redacted] in year 5 compared to the base case budget impact.

Table 43: Net budget impact for no reduction in drug costs for home infusions

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Elosulfase alfa available scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa not available scenario	£1,779,824	£1,832,785	£2,105,078	£2,174,291	£2,232,752
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ii. No reduction in drug costs for home infusions + 100% take up from year 2 onwards

In this scenario, 50 of the 88 patients receive treatment in the first year along with all the new born patients diagnosed that year. From the second year onwards, all 88 patients receive treatment in addition to all the newly diagnosed patients in these years. The results are presented in Table 44. As expected, the net budget impact increases by around [redacted] in year 1 to around [redacted] in year 5.

Table 44: Net budget impact for no reduction in drug costs for home infusions +100% take up in the following years

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Elosulfase alfa available scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa not available scenario	£1,779,824	£1,832,785	£2,105,078	£2,174,291	£2,232,752
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

iii. No reduction in drug costs for home infusions + 70% take up from year 2 onwards

In this scenario, 50 of the 88 patients receive treatment in the first year along with all the patients diagnosed that year. From the second year onwards, 62 patients receive treatment along with all the newly diagnosed patients in these years. The results (shown in Table 45) indicate that compared to the base case, the net budget impact increases in the first year but decreases substantially with following years.

Table 45: Net budget impact for no reduction in drug costs for home infusions +70% take up in the following years

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Elosulfase alfa available scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa not available scenario	£1,779,824	£1,832,785	£2,105,078	£2,174,291	£2,232,752
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG performed a scenario using patient numbers as estimated by NHS England. There was an estimated prevalent population of 77 with an incidence of 2.6 persons per year. It was also assumed that in the first year only 50% of the patients (N = 38.5) would receive the treatment. From the following year onwards, all the 77 patients would receive treatment along with the newly diagnosed patients in those years. The results (as presented in Table 46) shows that in such a scenario, the budget impact will decrease by approximately [redacted] in year 1 but will increase by approximately [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5 respectively, compared to the base case scenario.

Table 46: No reduction in drug costs for home infusions with number of patients receiving treatment as suggested by NHS England.

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Elosulfase Alfa Available Scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase Alfa Not Available Scenario	£1,560,078	£1,611,881	£1,856,265	£1,922,982	£1,980,288
Net Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6 Impact of the technology beyond direct health benefits and on the delivery of the specialised service.

The CS describes the potential non-health benefits to patients and their families and caregivers associated with elosulfase alfa (CS section 14.1). The discussion is informed by a survey of caregivers[35] and expert opinion, and no cost analyses are presented. The non-health benefits are assumed to occur based on the outcomes of the clinical effectiveness studies included in the CS. By reducing disease progression from effective treatment it is suggested that patients can remain in education and employment for longer; that caregivers can remain in employment for a longer period of time, and there will be less disruption to the education of siblings.

Cost savings are anticipated for three government services. In education savings may occur through reduction or postponement of classroom assistance and school building adaptation

(though the ERG suggests that some schools may already be designed / adapted for wheelchair users). The impact on local government budgets may be reduced if fewer adaptations are needed for patients' homes. It is also suggested that increased independence for patients will reduce the need for respite care and welfare payments. Furthermore, the CS suggests that patients and caregivers who remain in employment will continue to pay income tax to the Treasury.

The submission describes costs borne by the patient and their families and caregivers (CS section 14.3). These range from costs for specialist lightweight electric wheelchairs (typical cost estimated to be £5000), travel costs for frequent hospital visits, time off work for patients and carers, to costs for physiotherapy. The submission does not explicitly claim that these costs would be reduced or delayed as a result of treatment with elosulfase alpha. The ERG note that some of the costs, such as specialist bespoke clothes and shoes, may not necessarily be reduced as a result of treatment as the clinical effectiveness evidence for growth was limited (see Section 3.3).

To illustrate the impact on caregivers results are presented in the submission of a published international cross-sectional survey of primary caregivers, sponsored by the company[8] (CS section 14.4). Fifty six caregivers from Europe and South America participated, though none were from the UK. The study found that adult patients who always required a wheelchair needed markedly greater caregiving time than patients who only used a wheelchair when needed or who did not use a wheelchair (around 14 hours, 4 hours and 1-2 hours per day, respectively). In children there was only a small difference in caregiving time between wheelchair users and non-wheelchair users, though this was a significant amount of time - amounting to around 12 hours per day on weekdays and between 14 - 15 hours per day on weekends. The study publication also reports the proportion of daily activities requiring complete or moderate assistance from the caregiver and the impact on caregivers (e.g. physical and mental health, family and social life, finances, employment). These are summarised in CS section 7.1.2. Of note, only 53% of caregivers of adult patients and 46% of caregivers of children were working, and of these, only 21% and 11%, respectively, worked full-time. This evidence therefore suggests the potential benefit to carers, in terms of ability to work, that might be possible with effective treatment.

The company describes the ways in which treatment of MPS IVA with elosulfase alfa can be considered to have influenced technology innovation in the UK, stating that this may position the UK as an attractive environment within which to conduct rare diseases research. The submission notes that the majority of clinical trial centres are located in the UK, with most of the global expertise in treating the condition concentrated in this country. Furthermore, the Morqio A Registry Study (MARS) will be based in the UK and this will characterise the MPS IVA population and natural history, and evaluate long-term effectiveness and safety of elosulfase alfa. The company suggests that, due to the concentration of expertise in treating MPS IVA in the UK, particularly in the four specialist centres, only limited additional training may be required for health professionals to administer elosulfase alfa (CS section 15.1). The NHS England submission to NICE also states that additional staff training is not a substantial issue, however, as noted in Section 7, if treatment is to be delivered in local rather than specialist hospitals, training and new facilities will be needed.

7 Other submissions

The following is a summary of additional submissions received from a parent/carer, patient organisations, clinicians and NHS England.

Parent/carer perspective

The comments received from a parent / carer are wholly supportive about elosulfase alfa and its benefits. Caring for two children with the disease has resulted in one parent having to give up work. The lack of early diagnosis is an issue (rarely before age of 2 years) and means that early intervention is not possible. Prior to elosulfase alfa, treatment of MPS IVA was limited to supportive care and various surgical interventions. The submission describes the significant impact of the physical effects of MPS IVA, surgery, care needs and coping with school, university, work and socialising for the whole family. Participation in a clinical trial has meant huge commitments by the family, resulting in having to travel a long distance for treatment.

The family has expectations that the treatment will stop or reduce the rate of deterioration normally expected with the progression of MPS IVA, while expressing a fear that the drug may not become available in the long term. Other issues expressed are that it is difficult to objectively recall how the children were prior to treatment with elosulfase alfa and that treatment outcomes are confounded by changes in attitudes and maturity as the child gets older. However, treatment benefits are reported to include increased growth, reduced breathing

problems, reduced need for a C-PAP machine at night and a positive psychological effect. It is suggested that the increase in wheelchair use seen while on elosulfase alfa treatment was related to other factors (such as the size of the school building) rather than a deterioration in condition. It is stated that children are also receiving infusions at school and not just at home, enabling parents to work instead of having to be present at the infusion.

Patient organisation perspective

The submission by Save Babies UK offers to share patient testimonials, while the MPS Society summarises many testimonials in its submission, emphasising the positive aspects of patients' experience in taking part in elosulfase alfa clinical trials and their willingness to put up with risk of severe adverse events, as the treatment offers relief from constant fear of deterioration and death. The MPS society suggests that it offers support to 95% of MPS patients in the UK (all types of MPS) and knows all patients with a diagnosis of MPS IVA, equating currently to 88 patients according to their registry. The MPS Society receives unrestricted educational grants from six pharmaceutical companies.

The MPS Society suggests that delays in diagnosing MPS IVA are attributable to GPs' and paediatricians' lack of knowledge about this rare disease. While patients are usually diagnosed aged between 3 - 7 years, some are missed until later. The disease limits the quality of life of patients and places a tremendous burden on carers. It is suggested that 75% of patents do not reach 100cm in height, with normal size organs in a small body causing pain and fatigue. Suggested benefits of treatment with elosulfase alfa includes increased ability to walk further, making an important difference to being able to walk around home, into school or a restaurant. Stabilising disease progression enhances quality of life of the patient and employers are much more likely to employ a person whose disability is stable. While some patients have problems with regular cannulation, difficult veins or needle phobia, these can be overcome. Additional benefits after stabilisation of the disease with elosulfase alfa for the carer include a reduced caring role and relief from mental stress (i.e. the constant fear of the child/adult deteriorating and dying).

The MPS Society Children suggests that a small number of patients from the Pakistani community with severe infantile phenotype do not appear to have experienced such a positive impact of the technology. Save Babies UK points out that the UK is a signatory to United Nation

Convention on the Rights of the Child (which came into force in January 1992), which under Section 6, covers the health and welfare of children.

Clinician and NHS England perspective

According to the perspective of clinicians and NHS England, non-progression of the disease due to treatment with elosulfase alfa would be a very successful outcome. AEs related to the treatment are not a big issue as these can be managed. Some clinicians have high hopes and expectations for the drug, but others are more circumspect.

It is suggested that there are some slight geographic differences in availability of services available to patients with MPS IVA, though they are broadly similar across England. It is stated that some adults are not in active treatment and that not all patients want treatment with elosulfase alfa (it is unclear why this should be so or the kind of patient this refers to). It is pointed out that the treatment will not remove the need for cervical spinal fixation for instability of the bones in the neck (needed by almost all patients), surgery for hip/knees, or cardiac monitoring and valve surgery.

It is stated that prognosis is the same for all patients with MPS IVA and that there is a wide range of disease severity, but the rate of decline varies between subgroups. It is suggested that patients with the least severe disease are likely to benefit more from elosulfase alfa, as almost all patients with severe MPS IVA will be wheelchair dependent by early teens and unlikely to benefit in a readily measurable way from elosulfase alfa. Furthermore, it might be appropriate to identify patients with mutations/genotypes that are unlikely to respond to treatment and offer supportive treatment alone, though this may be seen as discriminatory.

It is advocated that MOR-004 does not necessarily reflect the potential benefit of early/pre-symptom treatment. The short duration of the trials included in the CS may not reliably indicate long term benefits of elosulfase alfa. The markers used to measure outcomes may plateau, rather than showing continued improvement over the longer term. Opinion is that delivery of elosulfase alfa will add significantly to the cost of the technology itself, additional demands on time, resources and lifestyle of patients (to accommodate weekly infusions), as well as NHS resources. The cost of delivering elosulfase alfa is currently borne by regional NHS authorities. The total budget for specialised services is £12 billion (2014/15), with no separate budget for highly specialised services. Clinical teams with experience of providing elosulfase alfa are

already in place, but if it is delivered in local rather than specialist hospitals, training, new facilities and accommodation for patients and carers will be needed. With more home infusions additional services, training and emergency equipment will be needed. The ideal would be outreach services to patients' homes, as the cost of home care would not be greatly increased with many patients already on other enzyme replacement therapies delivered at home.

8 DISCUSSION

8.1 Summary of clinical effectiveness issues

The CS presents evidence from a range of studies. There are limited randomised controlled trials in this area, with most of the presented studies being un-controlled studies. This leads to some difficulties in the interpretation of the results, particularly as MPS IVA is heterogeneous in its presentation. As such treatment effects seen have wide distributions around the mean estimates. Overall the results from the most methodologically reliable study, the MOR-004 RCT, were statistically significant on the primary outcome (6MWT) only. Results from the longer-term, uncontrolled studies, appear to show an effect of treatment, but without a comparator can only be compared with the natural history of MPS IVA.

It is also difficult to establish which patients will respond to treatment and which may not. Treatment with elosulfase alfa will be lifetime, and although the CS presents data for 72 weeks, there is no clear evidence of the effects or harms of the treatment over the life course of an individual with MPS IVA. The outcomes employed in the included studies were surrogate outcomes, which may have been subject to issues with their measurement, for example, their standardisation. It is also unclear how results from these outcomes can be interpreted.

8.2 Summary of issues for costs and health effects

The CS includes evidence on the cost and health effects of elosulfase alfa in MPS IVA patients compared to current standard care. The model structure and methods adopted for the economic evaluation are reasonable and generally appropriate. The model structure is consistent with the clinical pathway of the MPS IVA.

The ERG identified some assumptions which appear to overestimate the benefits of elosulfase alfa in patients with MPS IVA, including incorporating an additional utility increment and mortality benefit for patients treated with elosulfase alfa. In addition there is considerable

uncertainty around the long-term treatment effect on disease progression based upon the limited clinical evidence presented. Additional analyses have been presented by the ERG for changes to these assumptions and have a substantial impact on the model results.

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