NICE National Institute for Health and Care Excellence

Highly Specialise Technology

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology (HST)

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from BioMarin Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Rare Disease Research Partners submission
   b. The MPS Society submission
   c. RDRP/MPS society supporting document - Observations of elosulfase alfa treatment benefits in specialist lysosomal storage disorder centres in England. Unpublished report
   d. RDRP/MPS society supporting document - Patient and caregiver experience of treatment with elosulfase alfa under the managed access agreement. Unpublished report
   e. RDRP/MPS society supporting document - MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report
   f. RDRP/MPS society supporting document – The educational journey of individuals with MPS IVA Morquio disease. International MPS Symposium
   g. Birmingham Women's and Children's NHS Foundation Trust submission

4. **Evidence Review Group report** prepared by BMJ Technology Assessment Group (BMJ TAG)

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from BioMarin Pharmaceuticals

7. **Technical engagement responses and statements from experts:**
   a. Katy Brown, patient expert, nominated by The MPS Society
   b. Alex Morrison, patient expert, nominated by The MPS Society
   c. Sophie Thomas, patient expert, nominated by The MPS Society
   d. Elaine Murphy, clinical expert, nominated by British Inherited Metabolic Disease Group

8. **Technical engagement responses from consultees and commentators:**
   a. The MPS Society

b. MPS society supporting document - Multi-stakeholder engagement leading to access to treatment for MPS IVA (Morquio A) – a model for the ultra-rare disease community(
c. NHS England & Improvement

9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ Technology Assessment Group (BMJ TAG)

10. **Company additional information request** related to the company's preferred utility values prepared by BioMarin Pharmaceuticals

11. **Evidence Review Group post committee addendum** prepared by BMJ Technology Assessment Group (BMJ TAG)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Evaluation of elosulfase alfa for the treatment of mucopolysaccharidosis type IVA

Submission of evidence by BioMarin International Limited and BioMarin (U.K.) Limited

December 2020

Contents

Document key

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Information in highlighted black italic is to help the user complete the submission and may be deleted.

List of tables and figures

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Glossary of terms

Abbreviation	In full
1ry	Primary
1st	First
25FWT	25-foot walk test
2nd	Second
2ry	Secondary
3MSCT	Three-minute stair climb test
6MWT	Six-minute walk test
AB	Abstract
ADL	Activities of Daily Living
AE	Adverse Event
ANCOVA	Analysis of covariance
AP	Anteroposterior
APPT	Adolescent and Pediatric Pain Tool
ARG	Argentina
ASEBA	Aschenbach System of Empirically Based Assessment
AUS	Australia
BDI	Beck depression inventory
BiPAP	Bilevel Positive Airway Pressure
BL	Baseline
BL	Baseline
BMI	Body mass index
BMRN	BioMarin
BMT	Bone marrow transplant
BPI	Brief Pain Inventory
BRA	Brazil
BMJ	British Medical Association
C6S	Chondroitin 6 sulfate
CAN	Canada
CD	Caregiver domain
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-Effectiveness Analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Human Medicinal Products
CHO	Chinese Hamster Ovary
CLIN	Clinical
COL	Columbia
COMP	Comparator
CPAP	Continuous positive airway pressure
CRD	Centre for Reviews and Dissemination, University of York
DARE	Database of Abstracts of Reviews of Effects

Abbreviation	In full
DB	Double blind
DET	Data extraction table
DEU	Germany
DMC	Data monitoring committee
DNK	Denmark
DUP	Duplicate or copy publication
e1	Excluded on abstract screening
e1	Citation excluded at title/abstract screening stage
e2	Excluded on full paper screening
e2	Citation excluded at full text screening stage
EAP	Expanded access program
ECG	Electrocardiogram
EF	Ejection fraction
EMA	European Medicines Agency
ENG	England
EPAR	European Public Assessment Report
EQ-5D	Euroqol 5 dimensions
EQ-5D-3L	Euroqol 5 dimensions 3-levels
EQ-5D-5L	Euroqol 5 dimensions 5-levels
EQ-VAS	EuroQoL-5D visual analogue scale
ERT	Enzyme Replacement Therapy
ESA	Elosulfase alfa
ESHG	European Society of Human Genetics
ESP	Spain
EU-CTR	European Union Clinical Trials Register
EXT	Extension
FDA	United States Food and Drug Administration
FDT	Functional dexterity text
FEV1	Forced ejection volume in 1 minute
FP	Full Paper
FRA	France
FVC	Forced Vital Capacity
GAG	Glycosaminoglycan
GALNS	n-acetylgalactosamine-6-sulfate sulfatase
GPT	Grip and pinch test
HAE	Hypersensitivity adverse event
HAQ	Health Assessment Questionnaire
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HST	Highly Specialised Technologies
HTA	Health Technology Assessment
HTAD	Health Technology Assessment Database

Abbreviation	In full
i.v.	Intravenous
IAR	Infusion-associated reaction
IHE	Institute of Health Economics
INT	International
IQ	Intelligence quotient
ITA	Italy
ITT	Intention-to-treat
JPN	Japan
KS	Keratan sulfate
kg	Kilogram
KOR	Republic of Korea (South Korea)
L	Litres
LS	Least squares
LSDs	Lysosomal Storage Disorders
m	Metre
MA	Meta-analysis
MAA	Managed Access Agreement
MARS	Morquio A Registry Study
MAu	Marketing authorisation
MCID	Minimum clinically important difference
MeSH	Medical Subject Heading
mg	Milligram
mITT	Modified intention-to-treat
MIX	Mixed (population)
ml	Millilitre
MorCAP	Morquio Clinical Assessment Program
MPP	Modified per protocol
MPS	Mucopolysaccharidosis
MPS HAQ	Mucopolysaccharidosis Health Assessment Questionnaire
MPS IVA	Mucopolysaccharidosis type IVA (Morquio)
MRI	Magnetic Resonance Imaging
MSFC	Multiple sclerosis functional composite
Mths	Months
MVV	Maximal Voluntary Ventilation
N/A	Non-Applicable
NHS	National Health Service (UK)
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence (England & Wales)
NITT	Number of patients in intent-to-treat population
NLD	The Netherlands
NMA	Network meta-analysis
NmITT	Number of patients in modified intent-to-treat population

Abbreviation	In full
Norm	Normalised (for creatinine)
NR	Not Reported
OAE	Otoacoustic emissions
OBS	Observational study
OL	Open-label
OLE	Open-label extension
OUT	Outcome
PD	Pharmacodynamic
PedsQL	Paediatric quality-of-life
Ph	Phase
PI	Principal investigator
PK	Pharmacokinetic
PLA	Placebo
POP	Population
POR	Portugal
PRI	Puerto Rico
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PROS	Prospective
Pt	Patient
Pts	Patients
PUB	Publication
QA	Quality assessment
QAT	Qatar
QoL	Quality of life
qow	Every other week
qw	Weekly
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SAU	Saudi Arabia
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form-36
SOP	Standard Operating Procedure
SR	Systematic Review
SSIEM	Society for the Study of Inborn Errors of Metabolism
TA	Technology Appraisal
TUR	Turkey
Tx	Treatment
TWN	Taiwan
UK	United Kingdom
uKS	Urinary keratan sulphate

Abbreviation	In full
USA	United States of America
UTI	Urinary tract infection
VRA	Visual reinforcement audiometry
Wk	Week
Wks	Weeks
Yr	Year
Yrs	Years

Executive Summary

At the time of the original submission to NICE in December 2014 for the evaluation of elosulfase alfa, most trials were ongoing, including the extension study to the pivotal trial (MOR-004/MOR-005). The clinical trial programme has now closed, and the Morquio A Registry Study (MARS), which is an observational study, has since enrolled patients from the elosulfase alfa clinical trials as well as newly treated patients. As part of the conditional positive recommendation following the original NICE evaluation, a Managed Access Agreement (MAA) was put in place. Since December 2015, the MAA has systematically collected efficacy and safety outcomes data on a total cohort of [redacted] patients with MPS IVA as of the [redacted] data cut-off. Three patients have been excluded from the analysis ([redacted] patients were enrolled in the MAA but did not have follow-up data due to starting within a year of the analysis and one patient had duplicated records). [redacted] patients stopped treatment during the study period, however available assessments were included in the analysis: [redacted] voluntarily stopped for a variety of reasons ([redacted] patient left the country, [redacted] due to poor adherence or perceived lack of benefit) and [redacted] stopped due to failure to meet the criteria. Data from a total of [redacted] patients were therefore included in the analysis, including [redacted] ERT treatment-naïve patients who started treatment with elosulfase alfa only during the period of the MAA, and [redacted] patients who started treatment with elosulfase alfa prior to the MAA (i.e., they were enrolled in the clinical trial programme), and for whom both baseline and follow-up data were available.

A manuscript is expected to be published in Orphanet in early 2021 based on an earlier data cut-off of May 2019, including at that time [redacted] patients in the analysis, of which [redacted] were treatment-naïve and [redacted] were previously enrolled in the clinical trials in England. The results presented in the manuscript (May 2019 data cut) are consistent with the latest results ([redacted] data cut) presented in this addendum to the main company evidence submission.

Nature of the condition

Mucopolysaccharidosis type IVA (MPS IVA or Morquio A) is an ultra-rare, severely debilitating, multi-systemic, inherited disorder resulting in a significantly reduced life expectancy, if left untreated (Lavery and Hendriksz, 2015). The disease is characterised by the absence or reduction in N-acetylgalactosamine-6-sulfatase (GALNS) activity resulting in an accumulation of the glycoaminoglycans (GAG), keratan sulfate (KS) and chondroitin 6 sulfate (C6S). The progressive accumulation of these GAGs leads to significant morbidities and multi-systemic clinical impairments (respiratory, cardiac and musculoskeletal complications) resulting in premature mortality, diminished functional capacity and independence, decreased endurance and impaired quality of life (Hendriksz et al., 2014c, Hendriksz et al., 2014c, Akyol et al., 2019, Hendriksz, 2014). Life expectancy of patients not treated with elosulfase alfa is between 25 and 30 years (Lavery and Hendriksz, 2015), with fewer than 5% of patients living beyond 40 years of age without enzyme replacement therapy (ERT) (Montaño et al., 2007). Respiratory and cardiac complications are key drivers of mortality in patients with MPS IVA; respiratory failure is the most common cause of mortality accounting for 63% of patient deaths and cardiac dysfunction accounts for 15% of patient deaths (Lavery and Hendriksz, 2015). All affected patients experience significant functional limitations and reduced quality of life for patients, their caregivers and families (Harmatz et al., 2013, Hendriksz et al., 2014c).

The natural history of MPS IVA patients has been characterised in the Morquio A Clinical Assessment Program (MorCAP) study which was conducted in over 350 patients, estimated to represent ~10% of the total MPS IVA patients worldwide (Harmatz et al., 2013). The MorCAP study was a multicentre, multinational, cross-sectional and then subsequently longitudinal natural history study designed to describe the spectrum and progression of symptoms in ERT-untreated MPS IVA patients through direct clinical observation and assessments (Harmatz et al., 2013). Baseline data collected from the first 325 patients enrolled in the MorCAP study demonstrated substantial impairment in multiple domains including endurance, mobility,

respiratory function and growth (Harmatz et al., 2013). Musculoskeletal manifestations, including short stature, abnormal gait, genu valgum and pectus carinatum, were reported in more than 90% of MorCAP patients and contribute to the observed functional limitations. Wheelchair and walk aid use were found to be common among MorCAP subjects. The progressive reduction in endurance, increased reliance on wheelchairs and corresponding loss of independence have been highlighted as the key causes of patients suffering a poor quality of life (Hendriksz et al., 2014c, Lavery, 2014).

International guidelines for the management of MPS IVA (Akyol et al., 2019) recommend a comprehensive baseline assessment and continual re-evaluation of individual progress and patient goals based on measures that quantify this progress, including quality of life assessments. Elosulfase alfa enzyme replacement therapy is recommended for life.

Impact of the new technology

Elosulfase alfa (brand name: VIMIZIM®) is an enzyme-replacement therapy (ERT) and is a recombinant form of human N-acetylgalactosamine-6-sulfatase (sections 2.1 and 2.2). It is licensed in Europe, the US and Canada for the treatment of patients of all ages with Mucopolysaccharidosis type IVA (MPS IVA), otherwise known as Morquio A syndrome (section 3.1).

Elosulfase alfa provides the exogenous enzyme N-acetylgalactosamine-6-sulfatase that will be taken up into the lysosomes and increases the catabolism of the GAGs, KS and C6S. Enzyme uptake by cells into lysosomes is mediated by cation independent mannose-6-phosphate receptors leading to restored GALNS activity and clearance of KS and C6S (section 2.2).

Elosulfase alfa is available as a concentrate for solution for intravenous infusion in 5ml vials (section 2.3). Each vial of 5 ml contains 5 mg elosulfase alfa and the recommended dose is 2mg/kg of body weight, administered on a weekly basis. The NHS list price of a 5ml vial is £750 excluding VAT.

The efficacy and safety of elosulfase alfa are supported from data captured in a comprehensive clinical programme consisting of 7 clinical trials in 255 patients, as well as real world evidence collected in MPS IVA patients treated within real life clinical setting post approval. Clinical trials performed with elosulfase alfa assessed the impact of treatment on the systemic manifestations of MPS IVA in various domains including endurance, respiratory function, growth velocity, and mobility, as well as urine KS (SPC, 2014).

In the double blind, randomised, placebo-controlled Phase 3 study **(MOR-004)** of 176 heterogeneous patients diagnosed with MPS IVA, treatment with elosulfase alfa at the licensed dose of 2.0 mg/kg/week (QW) over a 24-week period had a statistically significant impact on the primary endpoint of 6-minute walk test (6MWT) distance at 24 weeks (mean 22.5 [95% CI 4.0, 40.9] metre improvement versus placebo, p = 0.017) (Hendriksz et al., 2014b). The duration of this study was limited to 24 weeks due to ethical considerations about withholding access to surgery. Patients were then enrolled into the MOR-005 follow-up study. Furthermore, patients treated weekly with elosulfase alfa showed numerical improvements in the 3-Minute Stair Climb Test (3MSCT) (in stairs/minute) compared with placebo at Week 24, but statistical significance was not reached possibly because of the lack of standardisation of test between centres, such as the availability of handrails, as well as the time frame being too short to demonstrate improvements in musculoskeletal complications. However, in the extension study MOR-005, sustained significant improvements in 3MSCT were observed. There was also a reduction of mean urinary KS by 40.7% (95% CI -49.0, -32.4) in QW dosing demonstrating a large and sustained pharmacodynamic effect of elosulfase alfa on abnormal KS lysosomal storage. Although MOR-004 was not designed to have sufficient power for any of the tertiary outcomes, subjects treated with the weekly dose of elosulfase alfa improved more than those receiving placebo, although the effect was not statistically significant. The largest treatment effects were seen in maximal voluntary ventilation (MVV), MPS-HAQ (particularly the mobility and caregiver domains), height, and growth rate. An analysis of the tertiary endpoints has been made to assess the

impact of elosulfase alfa on multiple domains in patients with MPS IVA (Hendriksz et al., 2015a). The analysis of a pre-specified composite endpoint (combining changes from baseline in 6MWT, 3MSCT and MVV z-scores equally weighted) showed a positive impact of elosulfase alfa QW versus placebo group (P = 0.053) (Hendriksz et al., 2015a).

In addition, the subgroup analyses in MOR-004 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/week dose regimen (P values for the test for interaction ranged from 0.1224 to 0.8921 for elosulfase alfa 2.0 mg/kg/week versus placebo).

Results from the phase 3 open-label extension study **(MOR-005)** show that the improvements observed in MOR-004 were sustained over a 120-week period. For patients treated at the licensed dosing regimen of 2.0mg/kg/week throughout the 120 weeks (QW-QW cohort), the mean (SE) change in 6MWT distance from pre-treatment baseline was 37.2 (7.9) m at 24 weeks, 30.7 (10.2) m at 72 weeks, and 32.0 (11.3) m at 120 weeks for the ITT population. Similarly, the mean (SE) changes from pre-treatment baseline in the 3MSCT for the QW-QW cohort were 4.6 (1.1), 5.0 (1.4), and 5.5 (1.9) stairs/min at 24, 72, and 120 weeks in the ITT population. Due to the absence of a placebo group, comparisons were performed on a matched population from the MorCAP natural history study in order to assess the significance of the sustained improvements in the MOR-005 extension study and provide context for interpretation of results. The comparison showed that, in contrast to the improvements seen in elosulfase alfa treated patients in the extension study, the natural history patients in the MorCAP study experienced constant uKS levels and a gradual decline in endurance test results over a similar period of time. The differences between the elosulfase alfa treated patients and the natural history study patients were significant for 6MWT, 3MSCT, and uKS outcomes (P < 0.05).

In addition, results from the **MOR-007** and **MOR-006** phase II studies indicate that treatment with elosulfase alfa is also effective in children under 5 years of age and patients with limited mobility, both subgroups of patients not studied

in the Phase 3 trial. In the MOR-007 and MOR-006 studies, treatment with elosulfase alfa led to a substantial and sustained decrease in mean normalised urine KS comparable to that seen in MOR-004 study population (Hendriksz et al., 2014b, Harmatz et al., 2017). Compared to an age-matched cohort of untreated children from MOR-001, children treated with elosulfase alfa in the MOR-007 study demonstrated a trend for favourable effects on growth. All these results support the need for early diagnosis and intervention with elosulfase alfa in order to delay disease progression and prevent, or delay, functional impairment (Ficicioglu et al., 2019b).

Recent real-world evidence is now also available from the MAA entered into with NHS England in 2015 and from the MARS registry study.

Latest MAA analysis, based on November 2019 data-cut (from BioMarin data on file) and including [redacted] patients with available assessments, shows results in [redacted] patients with MPS IVA who were initiated on treatment since 2015 and [redacted] patients who were previously enrolled in the elosulfase alfa clinical trial programme ([redacted] in MOR-002, and [redacted] in MOR-004, MOR-007 or MOR-008).

[redacted]

The newly initiated patients had the following improvements in:

- Endurance: mean (SD) 6MWT distance was [redacted] m at baseline and increased by [redacted] m ([redacted]%) to [redacted] m at last follow-up (n=[redacted]; mean treatment duration [redacted] years) (BioMarin MAA data on file). Baseline and/or follow-up data were not available for the remaining 11 patients at the time of the latest data-cut in November 2019;

- Pulmonary function: FVC and FEV1 were stable or numerically improved. In the age group of patients below 18 years old at baseline (mean treatment duration [redacted] years), percent change from baseline to the last follow-up was [redacted] for FVC and [redacted]

for FEV1. In the age group of patients who were 18 years old or older (mean treatment duration [redacted] years), percent change from baseline to the last follow-up was [redacted]% ([redacted]) for FVC and [redacted]% ([redacted]) for FEV1 (BioMarin MAA data on file);

- Cardiac function: All [redacted] patients who had ejection fraction measured at baseline had normal findings, and left ventricular ejection fraction (LVEF) remained within the normal range during the MAA (BioMarin MAA data on file);

- Reduction in uKS levels that were comparable to those seen in the clinical trials. Mean uKS decreased rapidly and remained stable over time thereafter; mean (SD) uKS was [redacted] ([redacted]) µg/mg creatinine at baseline and decreased to [redacted] ([redacted]) µg/mg creatinine at last follow-up in treatment-naïve patients (n =[redacted]; mean treatment duration [redacted] years) (BioMarin MAA data on file). Likewise, baseline and/or follow-up data were not available for the remaining 11 patients at the time of the latest data-cut in November 2019.

A substantial portion (n=[redacted] out of a total of [redacted] patients in the MAA) of patients in the MAA started treatment prior the MAA (i.e., in clinical trials), some of whom were in the original dose-finding trial for elosulfase alfa (n=[redacted]) and therefore have been on treatment over 10 years. These patients showed a maintenance of their endurance on average, and improvements in their lung function, indicating the durability of treatment (Mukherjee et al., 2019a, Mukherjee et al., 2020). In addition, the real-world data collected in the Morquio A Registry Study (MARS) demonstrated the positive outcomes of elosulfalse alfa treatment in a broader population and confirmed the durability of the benefit in the long-term (Mitchell et al., 2020).

The safety profile of elosulfase alfa is in line with safety profiles for other ERTs. The most common side effects seen in the clinical development programme were infusion related reactions, which were generally mild to moderate, and the frequency was higher during the first 12 weeks of treatment and tended to occur less frequently with time. The reactions were manageable

by infusion rate adjustments. No new safety concerns were identified in the real-world setting, both in MARS (Burton et al., 2020b, Burton et al., 2020a, PSUR, 2019) and in the MAA (BioMarin MAA data on file).

Value for money

Elosulfase alfa is currently the only pharmaceutical product available for the treatment of MPS IVA. The extensive clinical trial program, and the real-world evidence collected under the MAA show that the broad population of patients benefit from treatment by improving or stabilising their progressive disease.

The quality of life (measured by EQ-5D-5L) and activities of daily living data (measured by MPS-HAQ) collected also show that elosulfase alfa provides important benefits to patients, generally through improving scores for patients initiating treatment in the MAA, which remained stable over time in patients previously enrolled in clinical trials. MPS-HAQ data showed numerical improvements (i.e. decreases) across all domains up to 10 years (MOR-004/MOR-005, MAA): caregiver's burden, self-care, and mobility.

The cost-effectiveness model results presented in this dossier and based on the latest MAA outcomes data shows incremental quality-adjusted life years (QALYs) that are consistent with those presented in the first submission. Given that all patients have stabilised or improved in wheelchair use status, we have applied various scenarios to investigate different assumptions regarding long-term efficacy (see section 12.2.1).

In the base case scenario, MPS IVA patients receiving standard medical care generated 28.71 Life Years and [redacted] QALYs during their lifetime. If treated with elosulfase alfa as an add-on therapy, these numbers increased to [redacted] life years and [redacted] QALYs, resulting in health gains of [redacted] Life Years and [redacted] QALYs, respectively, and an incremental cost per QALY (ICER) of £[redacted].

When the 1.5% discount rate was applied to the effects, patients with MPS IVA who received standard medical care were estimated to have gained [redacted] life years and [redacted] QALYs. Patients treated with elosulfase alfa plus best

supportive care accrued [redacted] life years and [redacted] QALYs. This resulted in an incremental difference [redacted] life years, and [redacted] QALYs gained, and an incremental cost per QALY of £[redacted].

While all patients diagnosed with MPS IVA would in theory be eligible for treatment, it is estimated based on clinical expert opinion that on average in England, 4 newly diagnosed patients would start treatment each year; while, based on the MAA data, 1 patient would stop treatment each year. In addition, the MAA maintenance criteria have brought greater clarity on those who benefit less from treatment and therefore should be discontinued; these criteria are expected to continue to apply post-MAA. Therefore, the budget impact for patients with MPS IVA can be anticipated.

Impact of the technology beyond direct health benefits

MPS IVA has a significant impact on patients, caregivers and their families outside of the NHS/PSS, particularly in terms of education, employment and socialisation. Patients with MPS IVA experience constant challenges in life as regards mobility, pain, fatigue and an environment that is poorly adapted to their needs (Hendriksz et al., 2014c).

Patients and caregivers report a broad range of treatment effects that have an impact on their quality of life (Morrison and Fortune, 2020). In addition, increased energy and stamina and overall, being able to do more, is experienced by most patients on elosulfase alfa treatment (Morrison and Fortune, 2020).

As seen by stabilising patients who respond in the MAA, it is shown that treatment with elosulfase alfa helps keep patients and their primary caregivers in education or employment, improve the lives of siblings and lead to better socialisation for patients, their caregivers and families (section 14.1).

It is further anticipated that treatment with elosulfase alfa could result in cost savings to the following three government departments or budgets: Education, Welfare and Local Government (section 14.2).

Costs to the patient and their families, which are not reimbursed by the NHS/PSS, are considerable (section 14.3). Because of the extreme short stature typically manifested by patients with MPS IVA, together with the unique physical structure of patients and limited endurance with the disease, many ordinary everyday objects need to be adapted for use, all at the cost of the patient/family. These include: Adaptation of home and car; specialist bespoke clothes and shoes; cost of specialist lightweight electric wheelchairs; other specialist equipment to aid mobility, such as a bike or portable set of steps (section 14.3).

In addition, patients and their families incur substantial extra financial costs in terms of: Travel costs and hospital parking; additional time off work; additional support from carers and specialist childminders; the cost of private extra tuition; and physiotherapy and hydrotherapy sessions to relieve pain and address some of the symptoms of disease (section 14.3). The amount spent by family members in providing care is considerable (Hendriksz et al., 2014c) (section 14.4).

Conclusion

In summary, the real-world, long-term results of the MAA are consistent with the results from the extensive clinical trial programme and have shown that elosulfase alfa is well tolerated and provides sustained benefit across a number of clinical, quality of life, and activities of daily living measures. Evidence from the MAA over the last five years demonstrated that, in the broad majority of the population, elosulfase alfa stabilised patients' outcomes in quality of life, activities of daily life (ADL), and wheelchair status, and that endurance measured by the 6MWT remained stable in most patients (with some declining slightly with progression of the disease). These results also indicate that criteria used in the MAA for initiation and maintenance of treatment are appropriate.

For patients who were initiated to treatment in the MAA programme, results showed a rapid decrease after the first doses and a subsequent stabilisation over the long-term in uKS, as well as initial improvements in endurance and

pulmonary function and then stabilisation in these measures in the long-term. In addition, data showed that patients were not progressive in their dependency on a wheelchair and that their quality of life, pain, and ability to perform activities of daily life improved upon treatment initiation and remained stable in the long-term.

A number of patients (n=[redacted] out of [redacted] patients) in the MAA were in the original dose-finding trial MOR-002/100 for elosulfase alfa and therefore have been on treatment for about 10 years. These patients showed a maintenance of their quality of life, endurance for most of them, as well as improvements in their lung function, indicating the durability of treatment (see section 9.6.1.2.1).

Overall, the presented data provide further evidence that long-term treatment with elosulfase alfa has a positive impact on patients' quality of life and ability to perform activities of daily living and stabilises or slows down the progressive deterioration in endurance associated with the disease.

When compared to projected natural history data, treatment with elosulfase alfa has demonstrated meaningful improvements to all groups of patients with a confirmed diagnosis of MPS IVA. Finally, the results described above address the uncertainties on the long-term outcomes of elosulfase alfa pointed by The Committee in the first appraisal in 2015 (NICE, 2015b), confirming the clinical effectiveness of elosulfase alfa treatment.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 1. Statement of the decision problem (Table A1)

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Prospective new patients diagnosed with mucopolysaccharidosis type IVA	No change	n/a
Intervention	Elosulfase alfa (Vimizim®)	No change	n/a
Comparator(s)	Established clinical management without elosulfase alfa	No change	n/a
Outcomes	The outcome measures to be considered include: • endurance • mobility • respiratory and cardiac function • growth and development • vision and hearing sleep apnoea • fatigue • pain • mortality • adverse effects of treatment b • health-related quality of life (for patients and carers	Clinical outcomes: • Urinary keratan sulfate (uKS) • 6-minute walk test (6MWT) • Lung function (FVC, FEV1) • Ejection fraction (EF) • Antibody titres Quality of life/Activities of daily living: • MPS HAQ – Caregiver domain • EQ-5D • Adolescent and pediatric pain tool (APPT)/Brief Pain Inventory (BPI) • Beck Depression Index (BDI)	Specific outcomes agreed and measured as part of the MAA. The systematic review also captures outcomes broader than those measured in the MAA.
Subgroups to be considered	Existing MAA patients (see addendum report)	No change	n/a

Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life extent and nature of current treatment options	No change	n/a
Cost to the NHS and PSS, and Value for Money		Updated with current standard costs.	n/a
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service		Updated with information from the MPS Society.	n/a
Special considerations, including issues related to equality		No change.	n/a

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Approved name: Elosulfase alfa

Brand name: VIMIZIM®

Therapeutic class: Other alimentary tract and metabolism products, enzymes. ATC code: A16AB12

2.2 What is the principal mechanism of action of the technology?

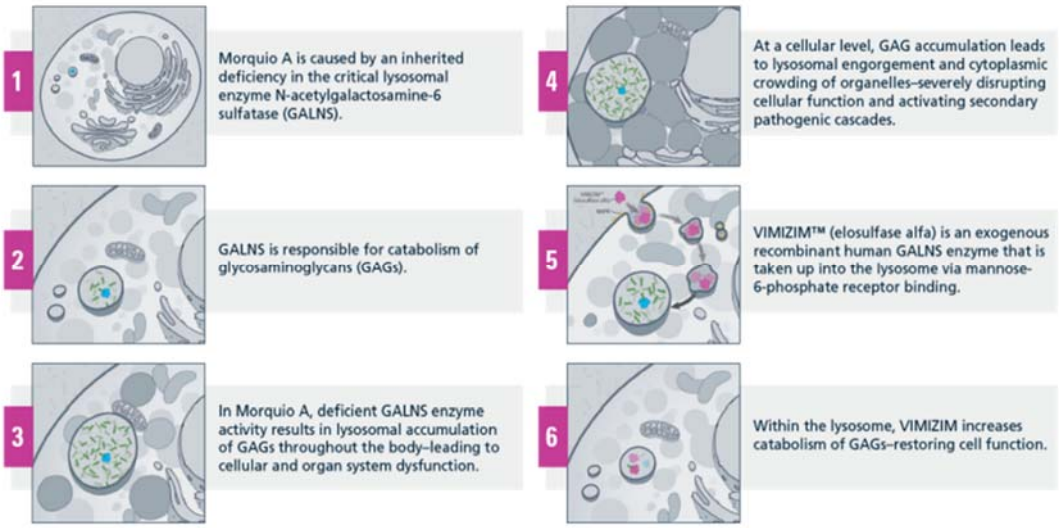
Mucopolysaccharidoses comprises a group of lysosomal storage disorders (LSDs) caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG).

Mucopolysaccharidosis type IVA (MPS IVA) is characterised by the absence or marked reduction in N-acetylgalactosamine-6-sulfatase (GALNS) activity. This activity deficiency results in the accumulation of the GAG substrates, keratan sulfate (KS) and chondroitin 6 sulfate (C6S), in the lysosomal compartment of cells throughout the body. The progressive accumulation of these GAGs leads to significant morbidities and multi-systemic clinical impairments (respiratory, cardiac and musculoskeletal complications) resulting in premature mortality, diminished functional capacity and independence, decreased endurance and impaired quality of life (Hendriksz et al., 2014c, Hendriksz et al., 2014c, Akyol et al., 2019).

Elosulfase alfa is a recombinant form of human N-acetylgalactosamine-6-sulfatase. Elosulfase alfa provides the exogenous enzyme N-acetylgalactosamine-6-sulfatase that will be taken up into the lysosomes and increases the catabolism of the GAGs KS and C6S. Enzyme uptake by cells into lysosomes is mediated by cation independent mannose-6-phosphate receptors leading to restored GALNS activity and clearance of KS and C6S.

The mechanism of action is shown visually in Figure 1.

Figure 1. Mechanism of action of elosulfase alfa in the catabolism of intracellular glycosaminoglycans



2.3 Please complete the table below.

Table 2. Dosing Information of technology being evaluated (Table A2)

Pharmaceutical formulation	Concentrate for solution for infusion. Each ml of solution contains 1 mg elosulfase alfa. Each vial of 5 ml contains 5 mg elosulfase alfa (SPC, 2014).
Method of administration	Intravenous infusion.
Doses	The recommended dose of elosulfase alfa is 2mg/kg of body weight (SPC, 2014).
Dosing frequency	The recommended dose of elosulfase alfa is administered once a week. The total volume of the infusion should be delivered over approximately 4 hours, although recommended infusion volumes and rates according to patient body weight are given in the SPC.
Average length of a course of treatment	As it is an enzyme-replacement therapy (ERT), patients with MPS IVA are expected to be treated with elosulfase alfa for the duration of their lives, subject to clinical judgement and/or the application of any protocols or criteria that would lead to a decision to discontinue treatment.
Anticipated average interval between courses of treatments	Not applicable.
Anticipated number of repeat courses of treatments	Not applicable.
Dose adjustments	No dose adjustments are envisaged in this patient population, although infusion volumes and rates according to patient body weight are listed in the SPC.

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Elosulfase alfa has a European marketing authorisation for the treatment of patients of all ages with mucopolysaccharidosis type IVA (MPS IVA), otherwise known as Morquio A syndrome. The marketing authorisation was received on 28th April 2014 and a copy of the current UK Summary of Product Characteristics (SPC) (SPC, 2014).

Prior to that date, on July 24th 2009, elosulfase alfa had been granted Orphan Drug designation by the European Medicines Agency (EMA) (EU/3/09/657) recognising its importance for the treatment of life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the European Union (EU).

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Not applicable.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Elosulfase alfa has widespread regulatory approval for the treatment of patients of all ages with MPS IVA. Please see Table 3 below for information on all approvals received up until December 2020.

Table 3. Worldwide regulatory approvals for elosulfase alfa

Country	Status	Submission Date	**Approval Date**
United States	Approved	29-Mar-2013	**14-Feb-2014**
European Union	Approved	23-Apr-2013	**28-Apr-2014**
Canada	Approved	25-Nov-2013	**2-Jul-2014**
Brazil	Approved	27-Jun-2013	**8-Dec-2014**

Australia	Approved	3-Oct-2013	**9-Dec-2014**
Japan	Approved	26-Mar-2014	**26-Dec-2014**
Mexico	Approved	10-Jan-2014	**7-Jan-2015**
South Korea	Approved	18-Jul-2014	**6-Feb-2015**
Chile	Approved	28-Aug-2014	**25-Feb-2015**
Hong Kong	Approved	23-Jun-2014	**26-Jun-2015**
Israel	Approved	6-Jul-2014	**13-Jul-2015**
Ukraine	Approved	21-Apr-2015	**19-Aug-2015**
New Zealand	Approved	18-Feb-2015	**20-Aug-2015**
Malaysia	Approved	31-Oct-2014	**28-Sep-2015**
Peru	Approved	25-May-2015	**4-Dec-2015**
Switzerland	Approved	20-Jan-2014	**19-Jan-2016**
Colombia	Approved	30-Apr-2015	**28-Mar-2016**
El Salvador	Approved	30-Nov-2015	**27-Apr-2016**
Serbia	Approved	29-Sep-2015	**21-Jul-2016**
Ecuador	Approved	18-Nov-2015	**22-Aug-2016**
Costa Rica	Approved	18-Dec-2015	**26-Sep-2016**
Taiwan	Approved	18-Jun-2015	**21-Jan-2017**
Thailand	Approved	12-Jan-2015	**4-Apr-2017**
Iran	Approved	17-Jul-2017	**10-Oct-2017**
Panama	Approved	30-Nov-2015	**16-Mar-2018**
Guatemala	Approved	27-Nov-2015	**12-Jul-2018**
Russia	Approved	23-Nov-2015	**22-Nov-2018**
Kazakhstan	Approved	27-Jul-2018	**25-Apr-2019**
Albania	Approved	21-Mar-2019	**17-May-2019**
China	Approved	8-Feb-2017	**21-May-2019**
Algeria	Approved	4-May-2016	**27-Nov-2019**
Argentina	Approved	30-Oct-2017	**07-Jan-2020**

3.4 If the technology has been launched in the UK provide information on the use in England.

Elosulfase alfa was granted a European marketing authorisation on the 28th April 2014 and has been available to patients in England and Wales since December 2015 under the terms of the Managed Access Agreement (MAA). The MAA was set up to evaluate the clinical effectiveness of elosulfase alfa in patients in England and Wales until December 2020; however, it has been extended by 12 months in agreement with NICE, NHSE, and BioMarin (see Appendix 5). Reimbursement of elosulfase alfa in patients with MPV IVA will be considered on the basis of the new evidence submitted in this dossier. In the meantime, the MAA is being amended and extended based on agreement with NICE, NHSE, and BioMarin in order to allow both existing and new patients to continue to access elosulfase alfa from 15 December 2020 until either: (i) publication of NICE final guidance for elosulfase alfa (HST2); (ii) or

termination of the MAA on 15 December 2021, whichever is earlier (see Appendix 5; extension contract not finalised).

UK withdrawal from the EU and regulatory impact

There will be a transition period until the end of 2020 while the UK and EU attempt to negotiate a future trading agreement ('the Implementation Period'). During this transition period, the current rules on trade, travel and business for both the UK and EU will continue to apply. Therefore, EU Centrally Authorised Product (CAP) Marketing Authorisations will not be converted to UK Marketing Applications until after the end of the Implementation Period, i.e. from 1st January 2021.

EMEA Number	Product	MAH	PL number
EMEA/H/C/002779	Vimizim 1 mg/ml - Concentrate for solution for infusion	BioMarin International Limited	PL 45814/0007

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

The efficacy of elosulfase alfa in the treatment of MPS IVA was demonstrated in the course of a clinical trial programme comprising 7 clinical trials that included 255 patients with MPS IVA. These studies are presented in Table 4. A description of the natural history study of the disease involving >350 patients (estimated to represent approximately 10% of the world's patient population) as well as the real-world evidence collected since regulatory approval is presented in Table 5. A list of all completed and ongoing clinical trials are presented in Table 6.

As mentioned above, at the time of the original submission to NICE in 2015 (NICE, 2015b), most of these trials were ongoing, including the extension study to the pivotal trial (MOR-004/MOR-005). The clinical trial programme has now completed, and the Morquio A Registry Study (MARS), which is an observational study, has since enrolled patients from the elosulfase alfa clinical trials as well as newly treated patients. The MAA, as part of the conditional NICE approval of elosulfase alfa, has systematically collected data on a cohort of [redacted] patients (as per the November 2019 data cut-off) with MPS IVA in England ([redacted] patients with available assessments included in the latest MAA analysis, of whom [redacted] initiated treatment during the period of the MAA) and these, together with the latest published information from the trials, is the focus of the dossier.

4.1.1. Clinical trial evidence

MOR-001 is a completed natural history study. MOR-001 was originally a cross-sectional study of patients with MPS IVA without limitations on age or

symptom severity, which began in 2008. However, the study was amended to be longitudinal in 2011. For inclusion into the study, individuals had a confirmed diagnosis of MPS IVA. Exclusion criteria included previous haemopoeitic stem cell transplant or a con-current disease or condition that would interfere with study participation. Data was available for more than 353 patients and was matched with MOR-004 patients to enable a comparison to natural history. To enable a comparison with MOR-005 study data, patients who underwent surgery and/or were less than 80% compliant were excluded from the analysis to reduce confounding (the MPP population, see section 9.4 for further description).

MOR-002 is a completed multi-centre, open label, Phase 1/2 dose escalation study with 20 MPS IVA patients in which three different doses of elosulfase alfa were successfully used in increasing strengths. The trial and the extension study showed no new safety issues.

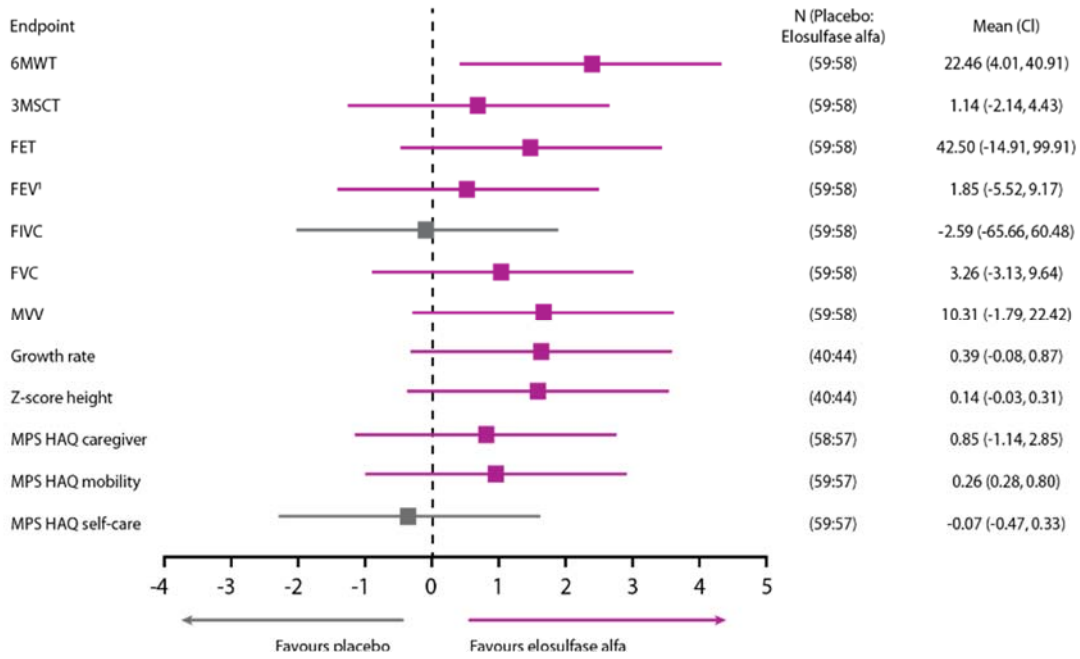
The pivotal phase 3 clinical trial was a multi-centre, randomised, double-blind, placebo-controlled study (**MOR-004**) (Hendriksz et al., 2014b). The MOR-004 study compared the effects of intravenous infusions of elosulfase alfa versus placebo over 24 weeks in MPS IVA patients who were aged between 5 and 57 years and able to walk between 30-325 meters to ensure changes in the primary endpoint in the 24-week timeframe could be observed. Given the confounding effects of orthopaedic surgery, surgical interventions during the study were not permitted. Hence, due to ethical considerations the treatment period was limited to 24 weeks. The reason for this is that these patients are so severely affected that they often need acute and planned surgery, and any further delay would be detrimental to their health. Therefore, it was deemed unethical to deny patients access to an operation for longer than was strictly necessary. Following discussions with regulatory agencies (namely the US Food and Drug Administration [FDA] and the EMA), 6MWT was chosen as the primary Phase 3 study endpoint because it is the only validated endpoint that can reliably show improvement within the 24-week study period and has been the basis for registration for ERTs for other LSDs. It also captures clinical and patient relevant beneficial changes across the diverse systems and organs

affected by MPS IVA, including the pulmonary, cardiovascular, nervous and musculoskeletal systems (Harmatz et al., 2006, Wraith et al., 2004, Butland et al., 1982, McDonald et al., 2020).

However due to the heterogeneity of the disease, endurance measures (such as the 6MWT) are unlikely to fully capture all the improvements in patients. Consequently, additional efficacy outcome measures of endurance (3MSCT), respiratory function, pharmacodynamic measures of urine keratan sulfate, activities of daily living and growth were included as secondary and tertiary endpoints in order to assess the impact of the treatment with elosulfase alfa across the broad range of disease related manifestations.

Given the long duration of exposure that would be required to identify statistically meaningful changes in these additional efficacy outcome measures, the study was powered only to show statistical significance for the primary endpoint (change from baseline in the 6MWT distance at week 24). However, the results from the other efficacy measures should provide directional evidence of the long-term effects in comparison to a natural history cohort (see Figure 2), which shows the treatment effect standardised by standard error in MOR-004.

Figure 2. Summary of efficacy endpoints (primary, secondary and tertiary) in MOR-004



CI, confidence interval; FET, forced expiratory time; FEV1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; HAQ, health assessment questionnaire; MVV, maximum voluntary ventilation; 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test.
Hendriksz CJ *et al*. *Mol Genet Metab* 2015; 114 (2): 178–185.

Patients who completed the MOR-004 study were eligible to enrol onto the open-label extension study (**MOR-005**), in which patients treated with placebo and 2mg/kg every other week (QOW) were transferred to 2mg/kg/week (QW) dosing of elosulfase alfa. The transitions continued until week 96 and depended on the time of enrolment. The details of the study design of MOR-004 and its extension MOR-005 are given in **Error! Reference source not found.**. To date, [redacted] patients from MOR-004/005 are currently treated in the MAA.

The published results of this study after 120 weeks of treatment (includes patients with up to 240 weeks of treatment) indicate continued and sustained improvement in endurance and pulmonary function of elosulfase alfa patients on the licensed dose (Hendriksz et al., 2016a, Hendriksz et al., 2016c). The publications also highlight a comparison to a similar natural history cohort of untreated patients from MOR-001, where the changes over the two years represent a significant improvement in endurance and pulmonary function over baseline versus untreated patients in the comparative MOR-001 group.

A number of Phase II studies have investigated the efficacy of elosulfase at 2.0 mg/kg/QW in patient cohorts outside those studied in the pivotal MOR-004/005 study. **MOR-006** was an investigation in patients with impaired mobility with a 6MWT ≤30 metres (N=13 patients) across a number of endpoints given the heterogeneity of this population, results indicated patients all showed different improvements with treatment across different endpoints (Harmatz et al., 2017). **MOR-007** was a Phase II study in 15 children under 5 and showed patients have improvement in growth versus similar natural history cohort and elosulfase alfa has shown an acceptable tolerability profile in children (Jones et al., 2015). Some of the patients from MOR-006 (n=[redacted]) and MOR-007 (n=[redacted]) were subsequently enrolled in the MAA and have been on treatment since then.

MOR-008 is Phase II study that investigated elosulfase alfa in patients over 7 years of age and with greater ambulation (6MWT≥200 meter [n=25 patients]) at doses of the indicated 2.0 mg/kg/QW and 4.0 mg/kg/QW and studied endurance and additional cardiopulmonary and pain endpoints in this more mobile population, results have shown improvements in pain and cardio-pulmonary end-points in the treated population (Burton et al., 2015). No patient from MOR-008 is currently treated in the MAA.

In addition to the comprehensive clinical programme, the long-term efficacy and safety data in a **real-world setting** are being collected in the Morquio A Registry Study (**MARS**; clinicaltrials.gov NCT02294877), an on-going multicentre, multinational, observational disease registry for patients diagnosed with MPS IVA. There are 325 patients from the clinical trials, MAA in England, and other countries who are enrolled in the MARS study and being followed-up for the collection of efficacy and safety outcomes until 2025.

Additional to the MARS study, in England, patients diagnosed with MPS IVA have had access to treatment with elosulfase alfa since December 2015 on a conditional basis through a **MAA,** where clinical and patient-reported outcomes of patients treated with elosulfase alfa have been collected to support the review of its clinical effectiveness at the end of the agreement period, initially in December 2020 but extended by 12 months in agreement with NICE, NHSE, and BioMarin. The data collection as part of the NICE re-evaluation process of elosulfase alfa has now been completed. During the Extension Period (until December 2021), PROs will no longer be collected for the purposes of the MAA, and NHSE/NICE will rely on clinician reporting to assess compliance with continuation criteria (via the Blueteq form). Analysis from the latest MAA data on file based on November 2019 data cut are presented in the following sections. A comprehensive publication in Orphanet based on an earlier data cut (May 2019) is expected to be available in the last quarter of 2020 outlining the results of patients treated with elosulfase alfa in England. Results are consistent with the latest MAA data and confirm that most patients continue to benefit from treatment with elosulfase alfa in the real-world over a long period of time (up to 10 years). Patients who were

initiated in the programme showed a rapid decrease and a subsequent stabilisation over the long term in uKS, as well as initial improvements in quality of life, activities of daily living, endurance and pulmonary function and then stabilisation in these measures in the long-term. The analysis also demonstrated that patients who have been on therapy over a long period are either maintaining initial benefits or continuing to see improvements in the broad majority of them, suggesting a positive impact on the natural history of MPS IVA.

Table 4. Description of clinical studies

Author and year of publication [ref]	Purpose of study (level of evidence) [ITT/PP]	Patients Number/Characteristics		Intervention and control	Follow-up period	Important endpoints
MOR-002 (Lorget et al., 2012)	phase 1/2, open-label, dose-response study	n=20	5-18 years	Elosulfase alfa 0.1 mg/kg/QW (weeks 1-12), 1.0 mg/kg/QW (weeks 13-24) and 2.0 mg/kg/QW (weeks 25-36)	48 weeks	6MWT, 3MSCT, FVC, MVV, urine KS and side effects
MOR-100 (Harmatz et al., 2015)	open-label extension study with patients from MOR-002	n=18	5-18 years	Elosulfase alfa 2.0 mg/kg/QW	72 weeks	6MWT, 3MSCT, FVC, MVV, urine KS, side effects and biochemical markers of bone and cartilage metabolism
MOR-004 (Hendriksz et al., 2014b)	phase 3, randomised, double-blind, placebo-controlled study	n=176	≥ 5 years	Elosulfase alfa 2.0 mg/kg/QW or QOW	24 weeks	6MWT, 3MSCT, urine KS concentration
MOR-005 (Hendriksz et al., 2016b, Hendriksz et al., 2016a)	open-label extension study with patients from MOR-004	n=173	≥ 5 years	Elosulfase alfa 2.0 mg/kg/QW or QOW	Up to 240 weeks	Side effects (number and seriousness), 6MWT, 3MSCT, urine KS concentration, and biochemical markers of bone and cartilage metabolism
MOR-006 (Harmatz et al., 2017)	phase 2, open-label study in patients with limited mobility	n=13	≥5 years	Elosulfase alfa 2.0 mg/kg/QW	48 weeks	FDT, GPT, 25FWT, BPI-short, APPT, PODCI, SF-36, lung function, sleep apnoea, KS concentration, cardiac function, growth, bone density, spinal cord morphology, pain medication, endurance, exercise capacity, and biochemical markers of bone and cartilage metabolism
MOR-007 (Jones et al., 2015)	phase 2, open-label study in young patients<5 years	n=15	<5 years	Elosulfase alfa 2.0 mg/kg/QW	52 weeks	Urine KS, growth, side effects
MOR-008 (Burton et al., 2015)	Phase 2, double-blind, pilot study of two doses of elosulfase alfa	N=25	≥ 7 years	Elosulfase alfa 2.0 mg/kg/QW Elosulfase alfa 4.0 mg/kg/QW	27 weeks	Safety, exercise capacity (cardiopulmonary exercise test (CPET)), lung function, pain, muscle strength

Table 5. Natural history and real-world evidence studies

Author and year of publication	Purpose of study (level of evidence)	Patient Number/ Characteristics		Intervention	Follow-up period	Important endpoints
MOR-001 (Harmatz et al., 2013, Harmatz et al., 2015)	Natural History Study	N=353	1-65 years	Standard of care	104 weeks	6MWT, 3MSCT, FVC, MVV, urine KS
Morquio A Registry Study (MARS)	Patient registry, includes sub-studies for MOR-004/005 and MOR-007	N=325	0-69 years	Vimizim and standard of care	10 years (currently in year 5)	Safety, 6MWT, FVC/FEV1, urine KS
Managed Access Agreement	Cohort study of English patients for conditional reimbursement	N=69	2-49 years	Vimizim	Four years	Urine KS, 6MWT, FVC/FEV1, Ejection Fraction, QoL/ADLs

Table 6. Completed and ongoing studies with ESA

Study	Phase	Country	Design	Age (yrs)	Title	N	Status	Results?	Outcomes	1ry Completion Date	Sponsor/ Collaborators
NCT03204370, BMRN58492 (NCT, 2019a)	N/A	FRA	OBS COHORT, PROS	18+	Natural History of Atypical Morquio A Disease	9	Recruiting	No	6MWT	Feb 1, 2020	GOIZET BMRN Association Aquitaine de Recherche Clinique en Rhumatologie
NCT02208661, IRB00072780, MAPLE (NCT, 2018)	N/A	USA	OBS COHORT, PROS	18+	Psychological Concomitants of Morquio A Syndrome - Longitudinal Effects of Enzyme Replacement Therapy (The MAPLE Study)	12	Completed	No	ASEBA SR, SF-36, BPI	Mar-18	Nadia Ali, PhD BMRN Emory University
NCT00884949, MOR-002 (NCT, 2014a)	Ph 1/2	UK	OL, non-randomised, single arm, interventional	5-18 yrs	A Study to Evaluate the Safety, Tolerability and Efficacy of BMN 110 in Subjects With	20	Completed	Yes	Tx-emergent AEs, Change From BL in 6MWT,	Feb-11	BMRN

Study	Phase	Country	Design	Age (yrs)	Title	N	Status	Results?	Outcomes	1ry Completion Date	Sponsor/ Collaborators
					Mucopolysaccharidosis IVA				Change From BL in 3MSCT, % Change From BL in uKS, MVV and FVC		
NCT01242111, MOR-100 (NCT, 2015)	Ph 1/2	UK	OL, single arm, interventional	All	A Study to Evaluate the Long-Term Efficacy and Safety of BMN 110 in Patients With Mucopolysaccharidosis IVA (Morquio A Syndrome)	20	Terminated	Yes	Safety, Change From BL in 6MWT and 3MST, % Change From BL in uKS, MVV, and in FVC	Jul-14	BMRN
NCT01275066, MOR-004|2010-020198-18|10/H1306/87|18972/0213/001-0001|2011_038#B201129|145240|2011-01-09|20110012889|0999935174 (NCT, 2014b)	Ph 3	USA, ARG, BRA, CAN, COL, DNK, FRA, DEU, ITA, JPN, KOR, NLD, POR, QAT, SAU, TWN, UK	RCT, quadruple-blind	5+	A Double-Blind Study to Evaluate the Efficacy and Safety of BMN 110 in Patients With Mucopolysaccharidosis IVA (Morquio A Syndrome)	177	Completed	Yes	Change From BL in Endurance (in 6MWT, 3MSC), % Change From BL in uKS Normalized for Urine Creatinine	Aug-12	BMRN
NCT01415427, MOR-005 (NCT, 2014c)	Ph 3	USA, ARG, BRA, CAN, DNK, FRA, DEU, ITA, JPN, KOR, NLD, NOR, POR, SAU, ESP, TWN, TUR, UK	RCT, quadruple-blind	5+	Long-Term Efficacy and Safety Extension Study of BMN 110 in Patients With Mucopolysaccharidosis IVA (Morquio A Syndrome)	173	Completed	Yes	Change From BL in 6MWT - ITT and MPP, Change From BL in 3MSCT - ITT and MPP,	June 16, 2016	BMRN

Study	Phase	Country	Design	Age (yrs)	Title	N	Status	Results?	Outcomes	1ry Completion Date	Sponsor/ Collaborators
									Change From BL in uKS - ITT and MPP		
NCT01697319, MOR-006|2011-005703-33 (NCT, 2016)	Ph 2	USA, DEU, UK	OL, single arm, interventional	5+	Efficacy and Safety Study of BMN 110 for Morquio A Syndrome Patients Who Have Limited Ambulation	16	Terminated	Yes	% Change From BL in Speed (FDT), Change From BL in Strength (GPT), % Change From BL in Speed (25FWT), % Change From BL in Normalized uKS	Oct-14	BMRN
NCT01515956, MOR-007 (NCT, 2017)	Ph 2	USA, ITA, TWN, UK	OL, single arm, interventional	<5 yrs	Study of BMN 110 in Pediatric Patients < 5 Years of Age With Mucopolysaccharidosis IVA (Morquio A Syndrome)	15	Completed	Yes	% Change From BL to Wk 52 in uKS, Change From BL in Normalized Growth Rate Z-Scores	Feb-16	BMRN
NCT01966029, MOR-AUS (NCT, 2019b)	Ph 3b	AUS	OL, single arm, interventional	All	BMN 110 Phase 3B in Australian Patients	13	Completed	No	Safety and efficacy	Jul-16	BMRN
NCT01858103, US EAP 110-503 (NCT, 2914d)	EAP	USA, PRI	EAP	All	BMN 110 US Expanded Access Program	NR	Approved for marketing	No	EAP	NR	BMRN

Abbreviations: 25FWT, 25-Foot Walk Test; 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; AE, Adverse Event; ARG, Argentina; ASEBA SR, Aschenbach System of Empirically Based Assessment Self-Report; AUS, Australia; BL, baseline; BMRN, BioMarin Pharmaceuticals; BPI, Brief Pain Inventory; BRA, Brazil; CAN, Canada; DEU, Germany; DNK, Denmark; EAP, Expanded Access Program; ESP, Spain; FDT, functional dexterity test; FRA, France; FVC, Forced Vital Capacity; GPT, Grip and Pinch Test; ITA, Italy; ITT, intention to treat; JPN, Japan; KOR, Republic of Korea; MPP, modified per protocol; MVV, Maximal Voluntary Ventilation; N/A, non-applicable; NLD, The Netherlands; NOR, Norway; NR, not reported; OBS, observational; OL, Open-Label; Ph, phase; POR, Portugal; PRI, Puerto Rico; PROS, Prospective; QAT, Qatar; RCT, randomised controlled trial; SAU, Saudi Arabia; TUR, Turkey; TWN, Taiwan; tx, treatment; UK, United Kingdom; uKS, urinary Keratan Sulfate; USA, United States of America

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

Not applicable.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

MPS IVA is an ultra-rare, multi-systemic and life-limiting disease. There is a real unmet medical need for these patients. Beyond treatment with elosulfase alfa, options focus on treating symptoms and providing supportive care only. Elosulfase alfa is the only treatment licensed for this group of patients that can impact the underlying cause of the disease by stabilising or slowing disease progression. Recently published international professional guidelines state that MPS IVA patients should be treated with elosulfase alfa as soon as the diagnosis has been confirmed (Akyol et al., 2019).

MPS IVA patients suffer from a range of disabilities and treatment with elosulfase alfa would be expected to reduce and/or delay the burden of disability in these patients.

All patients with MPS IVA will be able to benefit from treatment with elosulfase alsa, as there are no differences in benefit seen based on demographic characteristics (Mitchell et al., 2019b, Moisan et al., 2020). In the MAA, all patients benefited from treatment and those who experienced less benefit discontinued treatment based on the MAA maintenance criteria and these were often self-motivated.

5.2 How will the submission address these issues and any equality issues raised in the scope?

All patients in the MAA benefited from treatment with elosulfase alfa; the MAA had maintenance criteria in place, which clinically identified those who had less benefit and should discontinue treatment.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Mucopolysaccharidosis type IVA (MPS IVA or Morquio A syndrome) is an ultra-rare, severely debilitating, multi-systemic, and inherited disorder. The disease is characterised by the absence or marked reduction in GALNS activity, and this deficiency results in the accumulation of the GAG substrates, KS and C6S. These GAGs progressively accumulate in multiple body organs and tissues.

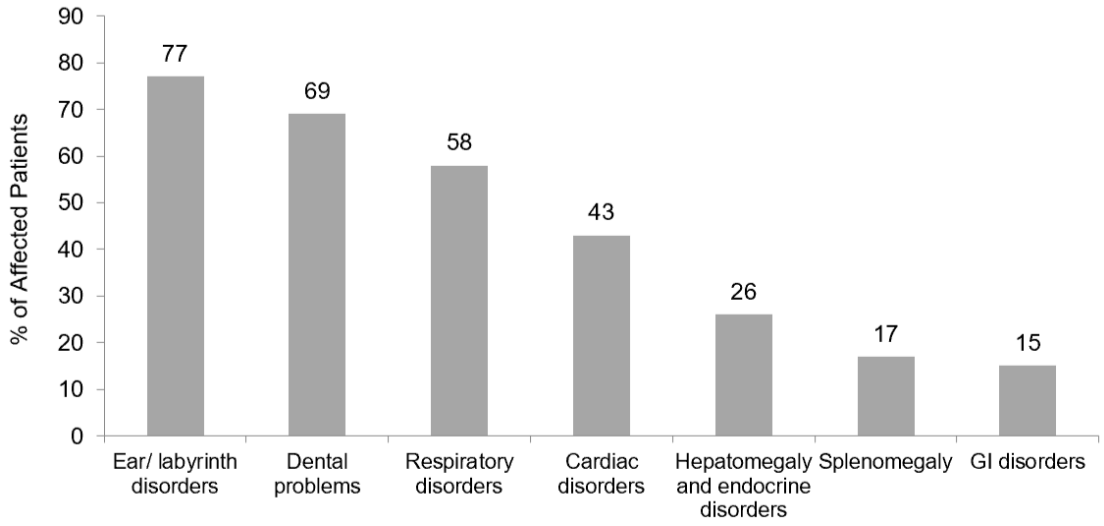
Patients appear normal at birth, but initial presenting symptoms often manifest in the early years of life. The progressive accumulation of these GAGs can lead to premature mortality (Lavery and Hendriksz, 2015) if patients are not treated early, significant morbidities and multi-systemic clinical impairments (respiratory, cardiac and musculoskeletal complications) resulting in diminished functional capacity, decreased endurance and impaired quality of life (Akyol et al., 2019).

Untreated patients generally die in their second or third decade of life (Harmatz et al., 2013, Lavery and Hendriksz, 2015), with fewer than 5% living beyond the age of 40 years (Montaño et al., 2007). Respiratory and cardiac complications are key drivers of mortality in patients with MPS IVA with respiratory failure accounting for 63% of patient deaths and cardiac dysfunction accounting for 15% of patient deaths (Lavery and Hendriksz, 2015, Tulebayeva et al., 2020).

Due to the large number of mutations that can cause MPS IVA, clinical manifestations of the disease are heterogeneous. Regardless of the specific clinical manifestation for each patient, all patients suffer a range of serious and debilitating morbidities. MPS IVA is one of the few MPS diseases that does not affect the brain (Tomatsu et al., 2011).

Studies by Harmatz et al (Harmatz et al., 2013, Harmatz et al., 2015) defined the natural history of untreated MPS IVA patients through direct clinical, radiographic and laboratory observation. The natural history study has been conducted in over 350 patients, which was estimated to represent ~10% of the world's MPS IVA population. This study described the spectrum of symptoms and progression of disease including impact on respiratory and cardiac function, growth, endurance, medical and surgical history, biochemical. Disease manifestation is heterogeneous, which is caused by the widespread distribution of GAG accumulation throughout cells in the body, but all forms manifest in severe disease with more than 220 different mutations of the GALNS gene identified (Morrone et al., 2014). The range of symptoms experienced by patients is presented in Figure 3.

Figure 3. Range of symptoms experienced by MPS IVA patients



Source: Harmatz et al, 2013

The data shows that patients suffer significant impairment across multiple domains (growth, endurance, respiratory function and quality of life

impairments). Skeletal deformities in MPS IVA patients are extremely common with the MorCAP study showing 71% of patients reporting surgical procedures. The progressive reduction in endurance, increased reliance on wheelchairs and corresponding loss of independence have been highlighted as the key causes of patients suffering a poor quality of life (Christian J. Hendriksz *et al.*, 2014; Hendriksz C *et al.*, 2014; Lavery and Hendriksz, 2015a).

MPS IVA patients require frequent surgeries and a significant amount of care. All patients suffer a range of serious and debilitating morbidities with the most frequent features being (Harmatz et al., 2013, Tomatsu et al., 2011):

- **Respiratory impairment**: Patients suffer from both obstructive and restrictive airway disease. GAG accumulation causes narrowing the airways and thoracic and spinal deformities impair normal respiratory movement of the rib cage (Tulebayeva et al., 2020, Hendriksz et al., 2014c);

- **Cardiovascular complications**: GAG accumulation leads to valvular insufficiency (mitral, aortic & tricuspid) often leading to cardiac hypertrophy and arrhythmias (Mohan et al., 2002, John et al., 1990, Vashakmadze et al., 2019);

- **Significantly reduced endurance**: caused by poor cardio-pulmonary function combined musculoskeletal manifestations (Harmatz et al., 2013);

- **Musculoskeletal impairments**: Multiple musculoskeletal complications occur including dwarfism, cervical spine instability, spinal cord compression (a major cause of disability and frequent surgical procedures) and multiple joint abnormalities (Genu Valgum, Coxa Valga, Hip Dysplasia) (Montaño *et al.*, 2008). Growth is severely affected with adult patients rarely reaching above 1.3m in height (Montaño *et al.*, 2008);

- **Frequent surgical procedures related to orthopaedic, ENT and respiratory issues** (Hendriksz, Lavery et al., 2014);
- **Eye, ear and dental impairments** (Hendriksz, Lavery et al., 2014);
- **Serious impacts on quality of life and high requirement for informal care**: MPS IVA patients suffer from increasing pain and fatigue, reducing endurance and diminishing functional capacity as they become older and more compromised, all of which result in an increasing dependence on a wheelchair; this results in a markedly reduced QoL and a greater need for informal care (personal assistant) (Hendriksz C *et al.*, 2014).

Respiratory impairment

Patients suffering from MPS IVA exhibit a reduction of respiratory capacity caused by the accumulation of GAGs in the connective tissues of airways, which leads to progressive pulmonary dysfunction (Tulebayeva et al., 2020). They may exhibit a restrictive respiratory pathology due to a direct obstruction of the upper or lower respiratory passages, cervical myelopathy or restriction of the thoracic cage (Hendriksz et al., 2013b, Tulebayeva et al., 2020). The patients in the registry study exhibited severely limited respiratory function. The considerable impairment of the respiratory function was associated with a multitude of other physical problems that affected the endurance of patients (Semenza and Pyeritz, 1988).

The mechanical obstacles of the respiratory passages lead to dyspnoea and recurrent respiratory infections and may progress to respiratory failure. Respiratory failure was the primary cause of death in nearly two-thirds of patients (Lavery and Hendriksz, 2015, Tulebayeva et al., 2020). The obstructive and restrictive respiratory pathologies predispose the patients to develop pneumonia and respiratory failure (Tulebayeva et al., 2020). The obstructive sleep apnoea syndrome may lead to prolonged periods of hypoxia and pulmonary hypertension and may cause death. Numerous patients need the use of respiratory assistance and of continuous positive-pressure ventilation, including oxygen supplementation and/or a tracheotomy in the

most severe cases of hypoxia (Hendriksz et al., 2013b, Berger et al., 2013). Among the patients of the MorCAP register (median age 11.6 years), 58% exhibited respiratory, thoracic and mediastinal disorders, including sleep apnoea, restrictive lung disease and lung and sinus infections, and 14% received a treatment for their restrictive lung disease (Hendriksz et al., 2013b).

The treatment of the respiratory impairment is variable, because of the underlying pathology. Tonsillectomy and excision of adenoid vegetations seem to be the primary surgeries in patients suffering from MPS IVA.

Musculoskeletal impairments

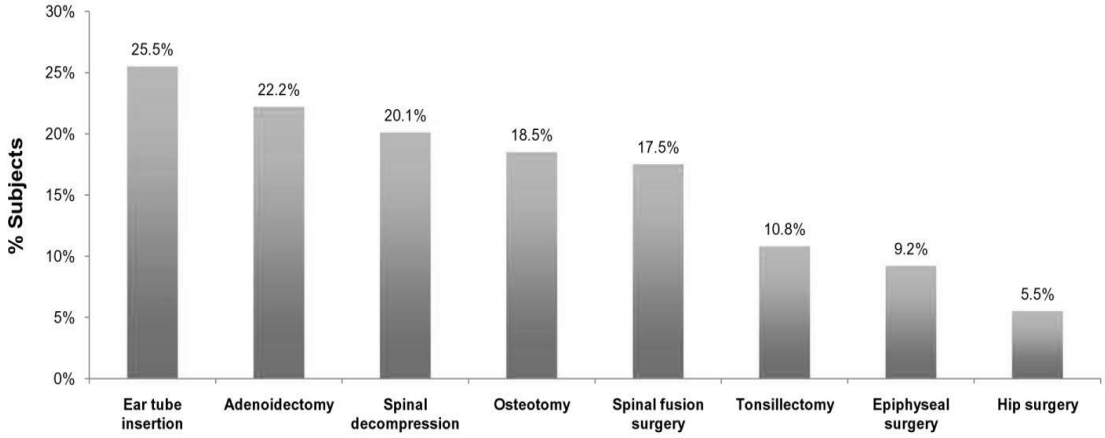
Patients suffering from MPS IVA are clinically distinguished from other patients suffering from MPS, because they do not exhibit a distorted appearance of the face or mental retardation. However, they exhibit distinguishing skeletal manifestations, such as spondyloepiphyseal dysplasia and joint instability (Hendriksz et al., 2013a).

Among the patients of the MorCAP register (Harmatz et al., 2013), the diagnoses of musculoskeletal disorders were the most frequent, with > 90% of the patients reporting an abnormal gait, genu valgum, small height and/or a small neck. Other frequently reported characteristics were joint laxity associated with stiffness and/or pain in > 80% of the patients and joint contractures and subluxations in 52% and 47% of the patients respectively.

Pectus carinatum, which is partly responsible for the limitation of the respiratory function, was reported in 97% of the patients (Hendriksz et al., 2013b). Anomalies of the spine were frequently reported, including kyphoscoliosis (85%), odontoid dysplasia (65%), lumbar lordosis (56%), instabilities of the cervical spine (49%), discopathies (23%). Preventive treatment includes arthrodesis and/or cervical decompression, currently a standard treatment, which has contributed to an improvement in the life expectancy of patients in the course of the last 10 years. Recommendations for spinal care in patients suffering from MPS IVA have recently been developed (Solanki et al., 2013).

In their medical histories, the majority of patients (71%) had undergone a surgical intervention as shown in
Figure 4.

Figure 4. Incidence of selected surgical procedures for all subjects



Source: Harmatz et al, 2013

Eye, ear and dental impairments

Eye: The opacity of the cornea may provoke vision disorders and photophobia. Among patients of the international Morquio A registry (Harmatz et al., 2013), 63% exhibited opacity of the cornea, including 22% with reduced visual acuity (20/80 or worse). There is currently no treatment capable of modifying the evolution of the vision disorders of patients suffering from MPS IVA. Corneal grafts in patients exhibiting progressive opacity of the cornea have been reported, with variable success measured by the recurrence rate.

Ear: MPS IVA leads to a reduction and even a loss of hearing. The loss of hearing, whether of transmission, of perception or mixed, is common in the first ten years of life (Riedner and Levin, 1977). The loss of hearing may have multiple causes, ranging from recurrent infections to structural deformations caused by the accumulation of GAGs. Transtympanic aerators are frequently implanted surgically in the course of the first 10 years of life, with variable success. Among the patients of the MorCAP register (Harmatz et al., 2013), 77% exhibited ear disorders, most frequently hearing impairments or moderate cases of otitis, and 25.5% had transtympanic aerators (Harmatz et al., 2013).

Dental disorders are frequent in patients suffering from MPS IVA. Among the patients of the MorCAP register (Harmatz et al., 2013), 69% exhibited dental disorders. Their severity varied considerably, and the typical clinical manifestations included widely spaced and splayed teeth, delicate and structurally weak enamel, pointed cuspids and shovel-shaped incisors. These anomalies of the enamel predispose the patients suffering from MPS IVA to dental caries.

Since the brain is not affected, MPS IVA patients retain normal intelligence and often achieve high levels of education.

The combination of respiratory function disorders, cardiovascular complications, small height, and musculoskeletal complications results in severely impaired endurance and functional capacity in patients with MPS IVA (Dhawale et al., 2013, Hendriksz et al., 2013b). Two-year longitudinal data (Harmatz et al., 2015) highlights the significantly reduced 6-minute walk test (6MWT) values; a matched phase 3 population from the MOR-004 study showed a progressive decline of 6.84m year-on-year in the 6MWT and has been described in more detail in the clinical programme (section 9.6). This population remains the largest cohort of untreated patients that has been followed until now. Since then, most patients have been on treatment with only very few treatment-naive patients remaining. A few of these untreated patients are followed in MARS, showing consistency with MORCAP natural history study within the limited data available.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

BioMarin has calculated that four new MPS IVA patients in England would be eligible for treatment per year. This is an estimation based on the actual number of new patients observed during period of the MAA.

It is estimated that the 63 patients currently treated with elosulfase alfa (as of December 2020) would remain on treatment. The number of new patients on elosulfase alfa has largely remained the same over the past five years; among the newly diagnosed patients initiated to elosulfase alfa in the MAA, there were 8 in 2017, 2 in 2018, 5 in 2019, and 5 in 2020 (including 4 patients not yet established on treatment do to COVID-19 treatment breaks), therefore it is estimated that, on average in England, 4 newly diagnosed patients could start treatment each year, while 1 patient will stop treatment.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

The progressive nature of the disease results in a much-reduced life expectancy for all patients. Death commonly occurs due to cardiorespiratory complications (Harmatz et al., 2013, Lavery and Hendriksz, 2015).

Untreated patients generally die in their second or third decade of life (Harmatz et al., 2013), and their life expectancy is drastically reduced to approximately 25.4 years (Lavery and Hendriksz, 2015). Fewer than 5% of the known patients with MPS IVA, according to the MorCAP baseline data, are above 40 years of age (Montaño et al., 2007).

A mortality study in the UK MPS IVA population evaluated the death certificates for 27 patients (15 male and 12 female) covering the period 1975-2010. The mean age at death was 25.30 (±17.43) years from 1975-2010, with female patients living longer than male patients (26.55 ± 12.28 years versus 22.95±17.63 years, respectively) (Lavery and Hendriksz, 2015).

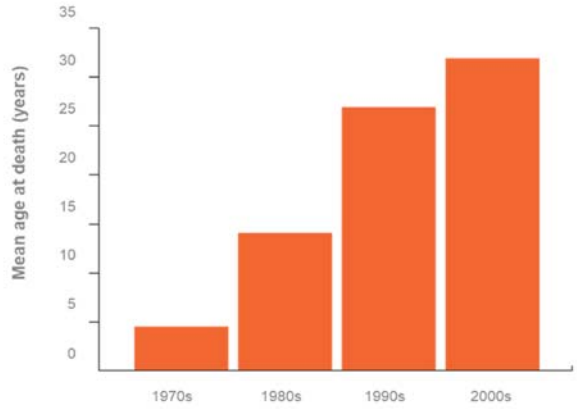
The main cause of death in 78% of patients was due to cardio-pulmonary complications before the age of 30 (Lavery and Hendriksz, 2015), including:

- Respiratory complications (in approx. 63% of the patients)
- Cardiovascular complications (in 15% of the patients);
- Post-traumatic organ failure and surgical complications, usually to the cervical spine (22%, where 11% of deaths are related to each).

Life expectancy increased gradually over time (R^2 = 0.0963) and mean age at death due to respiratory failure improved from 17.42±9.54 in the 1980s to 30.74±10.84 years in the 2000s. The authors suggested that improvements in multidisciplinary care, better surgical management of the cervical junction, which is increasingly becoming the standard of care, and referral of patients to specialist centres underlie this trend (Lavery and Hendriksz, 2015, Harmatz et al., 2013, Tomatsu et al., 2011) in Figure 5.

However, it is important to note that the publications mentioned above describe the life expectancy and disease burden of MPS IVA prior to the availability of elosulfase alfa in 2015 through the MAA. Therefore, it would be expected to observe improvements in mortality since the introduction of elosulfase alfa into the UK in 2015.

Figure 5. Historical life expectancy of patients with MPS IVA



Source: Harmatz et al., 2013; Tomatsu et al., 2011

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health,

emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

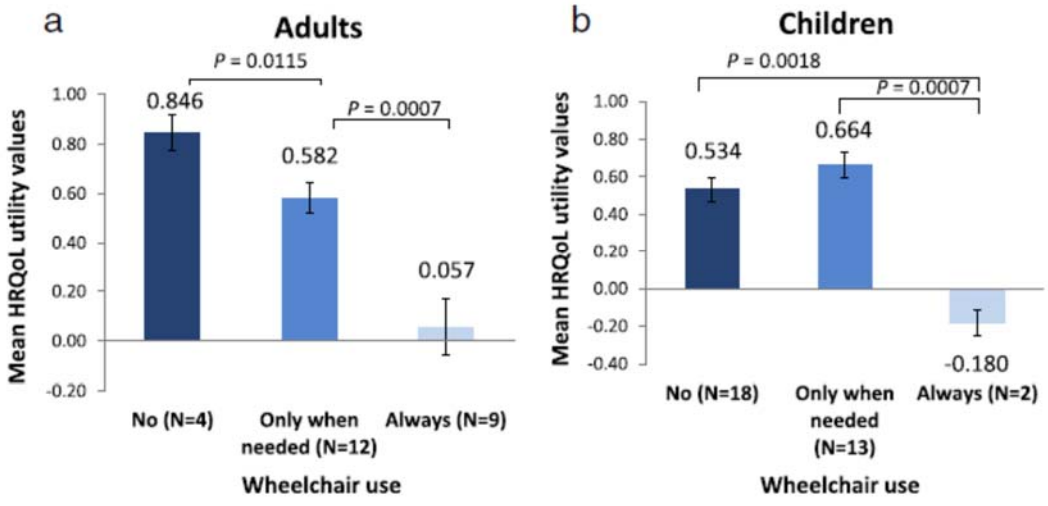
Over time, patients experience a progressive loss of endurance and an increase in pain and fatigue (Hendriksz et al., 2013b). Thus, in the longitudinal MOR-001 study, an annualised loss of 6.84 metres per year in the 6MWT was observed in a population matched to the Phase III population in MOR-004. The progressive loss of endurance, increase in pain and fatigue leads to increased dependence on wheelchair use, thus reducing patient quality of life and increasing the need for informal care (Hendriksz et al., 2014c).

The performance of various activities of daily living such as washing, making the bed and pouring a drink are impaired by hypermobility of the wrists, weakened grip and reduced shoulder movement. The MOR-001 study shows that 41% of the patients cannot cut their nails, 31% cannot tie their shoelaces, 22% cannot iron their shirts and 22% cannot open a jar. General endurance is greatly impaired because of a combination of muscle weakness, fatigue, pain and reduced ambulation. Children will often have a need to use a wheelchair and need increased informal support from this point on in their lives often leading to a poorer quality of life (Hendriksz et al., 2014c).

MPS IVA is associated with considerable burden of disease, which is accompanied by a reduced quality of life which deteriorates as the disease progresses and patients become older (Hendriksz et al., 2014c). Hendriksz et al investigated the patient reported burden of disease of MPS IVA syndrome in adults (≥ 18 years, n=27) and children (7-17 years, n=36). The study also investigated the impact of mobility, quality of life, pain and fatigue in patients with MPS IVA (Hendriksz et al., 2014c). Quality of life was measured by means of the general health-related quality of life (HRQoL) questionnaire EQ-5D-5L. Pain and its interference were measured by the Brief Pain Inventory Short Form (BPI-SF) in adults and the Adolescent Pediatric Pain Tool (APPT) in children. Fatigue was measured by asking patients about the number of evenings in the week they felt extremely tired.

The study results highlighted the heterogeneity in the clinical manifestations of disease reported by patients with MPS IVA. Most patients were severe, and the extent of their impaired endurance varied, they exhibited short stature, bone and joint disorders, an abnormal gait and eye problems, further highlighting the multi-systemic nature of the disease. Mobility was significantly reduced: 44% of children and 85% of adult patients used a wheelchair. A high level of wheelchair dependency caused a substantially reduced quality of life. Amongst adults this was primarily caused by lower scores in the areas of mobility, self-care and the performance of normal activities; pain was a key factor in reduced quality of life in children. The utility values for adults were 0.846 for those who did not use a wheelchair, 0.582 for those who used a wheelchair only when necessary and 0.057 for those who used a wheelchair all the time (Figure 6). For children these values were 0.534, 0.664 and –0.180 respectively (Hendriksz et al., 2014c).

Figure 6. HRQoL in adults (a) and children (b) by wheelchair status



Source: Hendriksz, Lavery et al. 2014c.

The authors concluded that the quality of life of patients with MPS IVA is related to remaining independent by retaining mobility and endurance, without being dependent on a wheelchair, but using a wheelchair as a tool to retain energy. Their quality of life falls drastically if patients need to use their wheelchair all the time, where their independence and personal confidence falls considerably (Hendriksz et al., 2014c). Even a slightly improved mobility whereby a wheelchair is used only when necessary significantly improves

quality of life and the patients' ability to continue to work and conduct daily activities. The maintenance of functional capacity, mobility, better management of pain and energy relates to an improved quality of life.

The study also investigated (n = 56) the additional burden for caregivers of patients with MPS IVA (Hendriksz et al., 2014c). The study found that adult patients who use a wheelchair all the time need assistance during virtually all their waking hours. Caregivers noted that patients with MPS IVA need full-time assistance from caregivers for 68% of their activities of daily living. Caregivers reported that there is a substantial reduction in the time they can devote to themselves and to others, including their partner, other family members and friends, which can have a significantly negative effect on their relationships. Caregivers also experienced (back) pain, stress and sleeplessness more frequently than the general population (Hendriksz et al., 2014c).

MPS IVA is therefore associated with severe multi-systemic complications leading to a high level of physical disabilities, which greatly impair patients' quality of life and ability to perform activities of daily living, while having a profound effect on those who care for them.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

In the short term, and as shown by the clinical studies presented in section 8 below, it is expected that treatment with weekly elosulfase alfa would lead to improved endurance, pulmonary function, and growth (in children), stabilisation of cardiac function, improvement in activities of daily living and improved quality of life in patients with MPS IVA (the latter particularly as a consequence of reduced wheelchair dependence and improved endurance).

The MPS-HAQ data from MARS and from the latest MAA results showed numerical improvements (i.e. decreases) across all domains – mobility, self-care, and caregiver domains – over 3 years. Data showed improvements in the short-term in the patients who were initiated on treatment during the MAA and a trend towards stabilisation over the long-term in patients who started treatment in the clinical trials, some of whom had been on treatment for up to 10 years (BioMarin MAA data on file). Results are further described in section 9.6.1.2.

These clinically meaningful benefits would translate into improved functional capacity, leading to more effective surgical interventions and greater ability for patients to recover quickly from orthopaedic surgeries, a reduced dependency on caregivers and an increased probability of patients and their carers to have and maintain employment and education. In the longer-term, these clinical benefits would translate into reduced mortality and longer life expectancy for patients with MPS IVA. Therefore, the treatment with elosulfase alfa is recommended to start as soon as possible after diagnosis, since the early initiation of therapy will likely change the course of disease (Akyol et al., 2019).

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

NICE, through the HST programme, provided guidance on elosulfase alfa for the treatment of MPS IVA in 2015. Relying largely on the Standard Operating Procedure (SOP) developed by the Lysosomal Storage Disorders Expert Group in 2014, care is managed at specialist centres (3 paediatric centres, and five adult centres). Management is patient needs-driven; given the heterogeneity of the condition, there is no one treatment pathway.

Care for these patients is in line with international guideline issued in 2019 (Akyol et al., 2019) and with the terms of the MAA set up in 2015 in England. MAA exclusion and starting criteria as well as treatment maintenance criteria are described in the below Table 8 and

Table 9, respectively.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

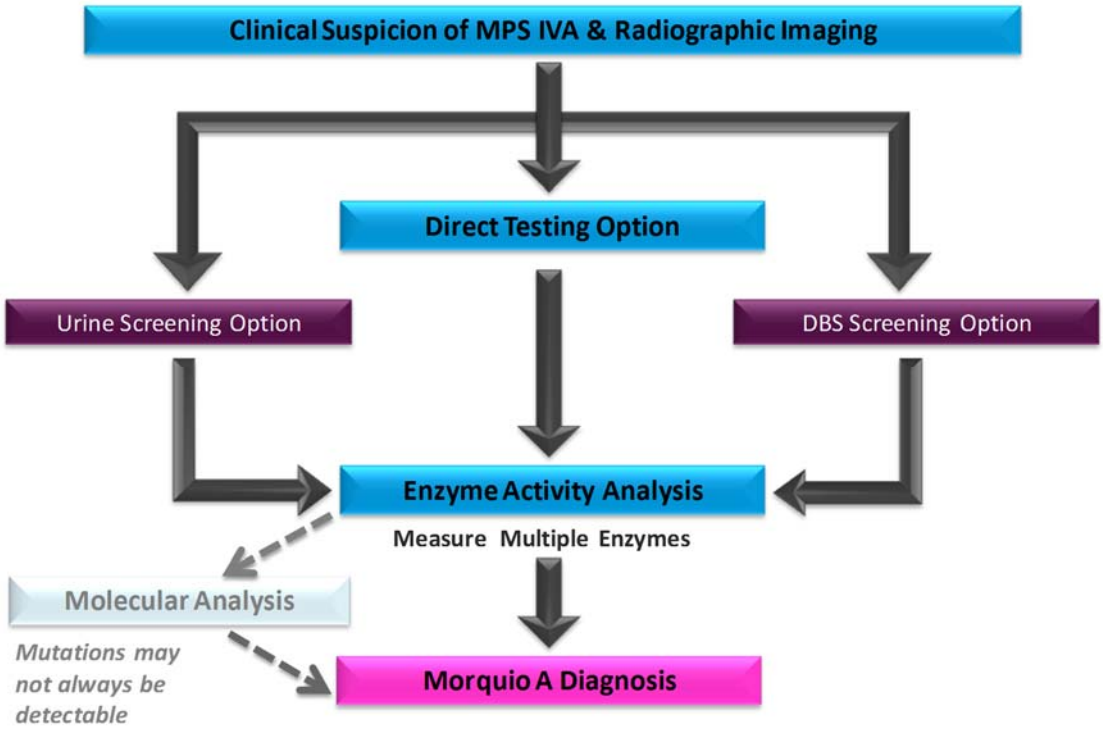
National centres of excellence

It is important to note that both the paediatric and adult metabolic units in Birmingham, Cambridge, London and Manchester are all designated national centres for the diagnosis and management of lysosomal storage disorders (LSDs). These centres are all involved in ongoing studies into the treatment and management of mucopolysaccharide diseases - including MPS IVA - and have extensive experience of ERTs. These regional centres all have an ongoing commitment to managing patients in dedicated outpatient and inpatient facilities.

Diagnosis

Diagnosis of MPS IVA in the UK is well-established through NHS laboratories with enzyme activity testing of GALNS using leukocytes or cultured dermal fibroblasts being essential for a definitive diagnosis. Molecular testing may also be used to confirm a diagnosis of MPS IVA; however, two known or probable causative mutations may not be identified in all cases of MPS IVA. A diagnostic testing algorithm has been published (Wood et al., 2013) to streamline this complex testing process (see Figure 7).

Figure 7. Algorithm for diagnosing MPS IVA



Source: Adapted from Wood et al 2013

Ongoing assessment

During the period of the MAA, the MAA Oversight Committee recommended that affected individuals with MPS IVA should be managed by a multidisciplinary team of health care providers given that it is a multi-systemic and progressive disease. The coordination of care was overseen by a specialist who had experience working with patients with LSDs, such as a geneticist or metabolic disease specialist. Once diagnosed, patients had to undergo regular comprehensive assessments (Patients should still undergo a baseline assessment prior to treatment initiation and regular follow-up assessments. However, the data collection as part of the NICE re-evaluation process of elosulfase alfa has now been completed. During the Extension Period (until December 2021), PROs will no longer be collected for the purposes of the MAA, and NHSE/NICE will rely on clinician reporting to assess compliance with maintenance criteria (via the Blueteq form).

Recommended assessments as per the MAA are summarised in **Error! Not a valid bookmark self-reference.** below and are aligned with the latest international guidelines (Akyol et al., 2019).

Table 7) for optimal outcomes with the frequency of clinic visits and assessments ideally tailored to meet the individual needs of each patient.

The clinical practice for MPS IVA is not expected to change following the end of the MAA. Patients should still undergo a baseline assessment prior to treatment initiation and regular follow-up assessments. However, the data collection as part of the NICE re-evaluation process of elosulfase alfa has now been completed. During the Extension Period (until December 2021), PROs will no longer be collected for the purposes of the MAA, and NHSE/NICE will rely on clinician reporting to assess compliance with maintenance criteria (via the Blueteq form).

Recommended assessments as per the MAA are summarised in **Error! Not a valid bookmark self-reference.** below and are aligned with the latest international guidelines (Akyol et al., 2019).

Table 7. Overview of assessments in the MAA

Assessments	Baseline	Month 4	Month 8	Month 12
6MWT or 25ft ambulation	X	X		X
FVC	X		X	
FEV1	X			
uKS	X	X		X
Cardiac echo (ejection fraction)	X			X
Missed infusions		X	X	X
Weight	X	X	X	X
Antibody titres	X		X	X
EQ-5D-5L	X			X
MPS-HAQ caregiver	X			X
Beck Depression Score	X		X	
BPI/ATTP	X	X	X	X

6MWT: 6-minute walk test; APPT: Adolescent Pediatric Pain Tool; BPI: Brief Pain Inventory; EQ-5D-5L: EuroQol 5 dimensions, 5 levels; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; MPS-HAQ: Mucopolysaccharidosis Health Assessment Questionnaire

Established clinical management

The only treatment available that is licensed for MPS IVA is elosulfase alfa. Besides elosulfase alsa, disease management options consist of supportive or palliative care, which include both medications and surgical interventions to relieve symptoms or address the complications of MPS IVA.

According to the SOP for England (2014 Lysosomal Storage Disorders Expert Group), medical treatment should focus on symptom control, preserving spinal cord health and function, optimising orthopaedic structure and function in hips and lower limbs, medical support for cardiac and respiratory function, maintaining optimal sensory function including hearing, sight and touch, and be directed towards improving the individual's quality of life.

Non-steroidal anti-inflammatory drugs have been administered for joint pain, antibiotics for pulmonary infection, and oxygen supplementation and CPAP/BiPAP for pulmonary compromise and obstructive sleep apnoea.

Surgical interventions include cervical spine fusion and/or decompression, spinal stabilisation, hip replacement, corrective knee and ankle surgery for severe genu valgum deformity, tonsillectomy/adenoidectomy, and cardiac valve replacement.

Surgeries in patients with MPS IVA are associated with various complications. In particular, the compromised respiratory function and cardiac abnormalities in MPS IVA patients can cause anaesthesia-related complications (Solanki et al., 2013), whereas cervical instability and myelopathy lead to a risk of paraplegia (Solanki et al., 2013).

However, clinical experts have observed that patients treated with elosulfase alfa in the MAA were now able to undergo more complex and effective surgical interventions with a quicker recovery from surgeries. These improvements in surgery can therefore lead to improved outcomes and reduced mortality from surgical complications (Lavery and Hendriksz, 2015).

Although some clinical benefit of haematopoietic stem cell transplantation (HSCT) has been reported in a handful of individual cases in patients with MPS IVA (Tomatsu et al., 2011, Algahim and Almassi, 2013), HSCT is also associated with high rates of morbidity and mortality due to infection, graft-versus-host disease, and other complications (Tomatsu et al., 2011). In view of the limited experience, lack of successful outcomes and the high morbidity associated with HSCT, this therapy is not currently recommended for treatment of MPS IVA.

The SOP for England (2014 Lysosomal Storage Disorders Expert Group) provides detailed recommendations on assessing and managing the following risks and complications of the disease:

- Anaesthetic risks
- Changes to bones and joints
- Cardiac disease
- Chest and respiratory infections
- Dental problems
- Growth retardation
- Hearing loss
- Hernias
- Hepatomegaly
- Neurological involvement
- Respiratory function
- Tonsils and adenoids
- Vision
- Quality of life/Activities of daily living

Treatment with elosulfase alfa

The accumulation of GAGs and KS begins early in the life of a patient with MPS IVA and is progressive and life-limiting. The early initiation of elosulfase alfa is therefore supported by the recent international guidelines published in 2019 (Akyol et al., 2019). Over the past five years, newly diagnosed patients with MPS IVA who were eligible for treatment (see MAA exclusion and starting criteria in Table 8 below) with elosulfase alfa have all been initiated on treatment under the MAA in England. The long-term, real-world data from the MAA and from MARS, which are consistent with the results from the pivotal clinical trial (MOR-004) and its open-label extension (MOR-005) (see section 9.6 below), demonstrate the importance of treating patients with MPS IVA with

elosulfase alfa as early as possible to prevent disease progression and preserve function.

The results from MOR-007 in a paediatric population also support the case for early treatment; the results demonstrated that early intervention with elosulfase alfa is well tolerated, produces a decrease in KS storage, and has shown a trend towards improvement in growth, which may lead to a long-term benefit in young patients.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

As mentioned above in section 8.2, clinical practice for MPS IVA is expected to remain unchanged at the end of the MAA period in December 2021. Although the MAA will no longer be in place, starting (Table 8) and maintenance criteria (

Table 9) for elosulfase alfa are expected to be continuously applied. In terms of assessments, patients should undergo a baseline assessment prior to treatment initiation and regular follow-up assessments during treatment.

Recommended assessments as per the MAA are summarised in Patients should still undergo a baseline assessment prior to treatment initiation and regular follow-up assessments. However, the data collection as part of the NICE re-evaluation process of elosulfase alfa has now been completed. During the Extension Period (until December 2021), PROs will no longer be collected for the purposes of the MAA, and NHSE/NICE will rely on clinician reporting to assess compliance with maintenance criteria (via the Blueteq form).

Recommended assessments as per the MAA are summarised in **Error! Not a valid bookmark self-reference.** below and are aligned with the latest international guidelines (Akyol et al., 2019).

Table 7 above and are aligned with the latest international guidelines (Akyol et al., 2019).

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Initiating treatment with elosulfase alfa as soon as possible after diagnosis of MPS IVA is expected to provide maximal benefit to patients, both by improving existing symptoms and minimising further disease-related impairments. Recently published international and professional guidelines state that MPS IVA patients should be treated with elosulfase alfa as soon as the diagnosis has been confirmed (Hendriksz et al., 2014b, Akyol et al., 2019).

Elosulfase alfa is the only treatment licensed for MPS IVA, and available to patients in England through the MAA, that has demonstrated a positive impact on stabilising or slowing down the progression of the disease. Therefore, pathway of care is expected to remain unchanged after the end of the MAA, with continued use of the starting (Table 8) and maintenance criteria (

Table 9).

‘Starting and maintenance’ criteria from the MAA

Table 8 and

Table 9 present the exclusion and starting criteria and the criteria for maintaining treatment described in the MAA, respectively.

Table 8. Exclusion and starting criteria of the MAA

Elosulfase alfa will not be started if any of the following apply: • The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long-term benefit (e.g. cancer or multiple sclerosis); or • The patient has a lung capacity (forced vital capacity) of <0.3 L and requires ventilator assistance; or • The patient is unwilling to comply with the associated monitoring criteria: o All patients are required to attend their clinics three times a year for assessment o All patients will sign up to the 'Managed Access Patient Agreement' (NICE, 2015)
All of the following are required before treatment is started: • All patients must have a confirmed diagnosis of MPS IVA as per the diagnosis criteria recommended in (Wood et al., 2013) • All patients must have confirmed enzymatic test, elevated urinary keratan sulfate and mutation analysis • In addition, patients aged ≥5 years can only start once a full set of baseline assessments has been obtained, and they have signed the Managed Access Patient Agreement

Table 9. MAA criteria for maintaining treatment

Clinical criteria (for treatment-naïve patients):

- Improvement in 6MWT distance or the timed 25-foot (7.6 m) walk (T25FW) of ≥10% over baseline or stabilisation after 10% improvement
- Improvement in FVC or FEV_1 of ≥5% over baseline or stabilisation after 1 year
- Decline in LVEF of <10% from baseline
- Decline of uKS of ≥20% from baseline (and stabilised)

Ex-trial patients

- 6MWT or T25FW remains ≥5% above the baseline value at the start of treatment
- FVC and FEV1 remain ≥2% above the baseline value at the start of treatment
- uKS levels remain reduced ≥20% from baseline
- Decline in LVEF of <10% from baseline

PRO criteria (for treatment-naïve patients and ex-trial patients):

- No adverse change in numerical value of two out of three of the following:
    - EQ-5D-5L score OR MPS-HAQ Caregiver Burden score
    - Beck Depression Score (≥13 years)
    - APPT / BPI pain severity score (depending on age)

6MWT: 6-minute walk test; APPT: Adolescent Pediatric Pain Tool; BPI: Brief Pain Inventory; EQ-5D-5L: EuroQol 5 dimensions, 5 levels; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MPS-HAQ: MPS Health Assessment Questionnaire; PRO: patient-reported outcome; uKS: urinary keratan sulfate

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

MPS IVA is a progressive and serious disorder causing extensive morbidity and early mortality (Lavery and Hendriksz, 2015), if left untreated. The clinical presentation of MPS IVA is very heterogeneous (Harmatz et al., 2013, Montaño et al., 2007).

As noted in section 8.2 above, the only treatment available for MPS IVA is elosulfase alfa. Besides elosulfase alfa, other available management options consist of supportive or palliative care, which includes both medications and surgical interventions to relieve symptoms or address the complications of MPS IVA. Surgical interventions especially are associated with complications and increased morbidity/mortality.

Elosulfase alfa is innovative and continues to be an effective treatment, as demonstrated by the long-term, real-world data in the MAA, in the management of this multi-systemic, life-limiting condition because:

- It is the only pharmacological treatment approved for the treatment of MPS-IVA and is approved for use in MPS IVA patients of all ages;
- Elosulfase alfa is the only treatment option (pharmacological or otherwise) that addresses the underlying biological cause of this severe, progressive and life-limiting disease. Elosulfase alfa is an ERT; the goal of ERT in MPS IVA is to replace the deficient GALNS, reduce the accumulation of GAGs at cellular level and ultimately restore cellular function;
- It is the first treatment option that has a positive impact on patients' quality of life in MPS IVA by stabilising or slowing down the progression of the disease; real-world data from the MAA and MARS studies has demonstrated the long-term safety and effectiveness of elosulfase alfa across different patient subgroups, and has brought greater clarity on those patients who benefit most from treatment. The treatment maintenance criteria defined for patients enrolled in the MAA (Table 9) ensured that only patients who are benefiting from the elosulfase alfa would continue to receive the therapy.
- Finally, it is the only treatment indicated for MPS IVA that has demonstrated significant improvements in growth for patients who are treated early compared to current clinical care, as shown in the clinical trial MOR-007 (results are reported in Table 39 and section 9.8.2). MPS IVA patients have normal-sized organs which, because of their attenuated growth and short stature, are housed within a confined space. Improvements in growth can, therefore, be associated with improved pulmonary function and endurance in

these patients. Early intervention with elosulfase alfa may help to ameliorate the impact of this disorder on growth.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Elosulfase alfa is already administered to patients with MPS IVA in England, under the MAA. Following specialist initiation and stabilisation of the patient on elosulfase alfa, the infusion is then delivered in a homecare setting by a trained nurse as is standard practice for the administration of other ERTs in the UK (Finnigan et al., 2018, National Homecare Medicine Committee, 2020).

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

None are anticipated over and above what would be required in using any new ERT.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

The data collection from the MAA for elosulfase alfa as part of the NICE re-evaluation process has now been completed. During the Extension Period (until December 2021), PROs will no longer be collected for the purposes of the MAA, and NHSE/NICE will rely on clinician reporting to assess compliance with continuation criteria (via the Blueteq form).

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Longer-term evidence from the MAA and from the MARS registry shows that elosulfase alfa has a positive impact on patients' quality of life and ability to perform activities of the daily life by stabilising or slowing down the progression of the disease. Whilst there is little evidence from the MAA on whether the number of surgical interventions has decreased, patients can now undergo more complex surgery with faster recovery and decreased risks of surgical complications.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

This section outlines the completed clinical trial data as well as the data collected during the MAA. As the most relevant data to this submission, the MAA information can be found in the sections noted here:

Academic in confidence data (**Fully redacted in this version** [redacted]): Full analysis of the MAA dataset in section 9.6.1.2.1 – Long-term outcomes from patients initiated under the MAA in England (analysis based on latest data cut-off from November 2019)

The following table provide quick access to the complete list of relevant studies described in this section:

Study	Cross-reference to section 9.4 (summary of methodology)	Cross-reference to section 9.6 (results of relevant studies)
MOR-004	Table 16	**Error! Reference source not found.**
MOR-005	Table 16**Error! Reference source not found.**	Table 35
MOR-002	Table 17	Table 36
MOR-100	Table 17	Table 37
MOR-006	Table 19	Table 38
MOR-007	Table 21	Table 39

MOR-008	Table 23	Results described in section 9.8.2
MAA	Table 24	See section 1809.6.1.2.1
MARS	**Study design**	See section 9.6.1.2.2
Other observational studies	Table 26 to Table 29	

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A clinical systematic review (SR) was conducted in November 2019 for the NICE submission for existing MAA patients in February 2020. The methods were documented in a protocol (MPSIVA_SRs_Protocol_v1.1_20191008.docx) in line with PRISMA-P requirements (Moher et al., 2015).

Appendix 1: Search strategy for clinical evidence (clinical SR) and

Appendix 2: Search strategy for adverse events (safety SR) detail the systematic searches performed to identify relevant clinical evidence. The search strategies and complete search strings are reported in these appendices.

The research question was as follows:

- What randomised, non-randomised or single arm studies/case series have been conducted with elosulfase alfa in Morquio A, published or as yet unpublished?

An updated search was conducted in November 2020 to assess if any new articles had been published since the last SR in November 2019. The search terms and inclusion/ exclusion criteria were the same as the original search of November 2019. The new search generated 84 articles at the 1st pass (EMBASE/ MEDLINE and 11 papers of other note), and 10 articles after the 2nd pass, which are reported separately from the main SR report.

For the clinical SR, key sources included: Embase, Medline, Medline in Process/e-publications ahead of print (via PubMed), the Cochrane Library (CENTRAL, CDSR) and Database of Abstracts of Reviews of Effects (DARE) (Centre for Reviews and Dissemination, University of York (CRD)), last 2 years (yrs) of Society for the Study of Inborn Errors of Metabolism (SSIEM) conferences and of the WORLD Symposium (2018/2019), systematic review and meta-analysis reference lists, included trials reference lists, any supplemental Google search to identify full texts of abstracts identified in electronic searching, e-alerts from the PubMed search tracked until 13 November 2019 and cross-referencing from the economic and utilities SRs.

To identify non-RCTs, extension studies, registry data, case-control studies and case-series, a bespoke string was developed, based on the British Medical Journal's (BMJ) search filter to identify cohort studies, case-control studies and case-series.

The BMJ filter is as follows:

1. exp cohort analysis/

2. exp longitudinal study/

3. exp prospective study/

4. exp follow up/

5. cohort$.tw.

6. exp case control study/

7. (case$ and control$).tw.

8. exp case study/

9. (case$ and series).tw.

Our adapted filter includes the BMJ filter, amended to Embase.com format:

'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'case control study'/exp OR 'case study'/exp OR (cohort OR (case* AND control*) OR (case* AND series)):de,ab,ti*

Plus additional terms for extension studies and registry data:

(extension NEAR/3 (trial OR study OR studies OR phase)):ab,ti*

'register'/exp OR 'disease registry'/exp OR (register OR registry):ab,ti

The search strings were unlimited by date. During screening, relevant recent SRs were selected for bibliography reference checks.

The search string combines:

MPS IVA terms AND study design terms

Conference reviews, chapters, editorials, letters, notes and case reports are then excluded from the string.

The usual method for excluding non-human studies was not used, as it has been noted that articles can be wrongly excluded if only indexed as non-human. Therefore, non-human articles were excluded more conservatively, with a specific bespoke filter using rodent terms in the title.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Strategies to retrieve clinical data from unpublished sources were as follows:

ClinicalTrials.gov was searched (https://clinicaltrials.gov/). One hundred and eighty studies were identified with the search terms (morquio OR MPS IV OR MPS IV A OR MPS IVA OR mucopolysaccharidosis IV OR mucopolysaccharidosis IVA), without any other restrictions. Relevant registry records were then checked for results having been posted.

During electronic searching, the links of registry records (e.g. to the European Union Clinical Trials Register (EU-CTR)) were checked for results having been posted.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

The inclusion and exclusion criteria used to select studies from the literature are summarised in Table 10 and Table 11 below:

Table 10. Inclusion criteria used for clinical studies (C1 Table)

Characteristic	Inclusion criteria
Population	MPS IVA (Morquio syndrome) Any age group (children or adults)
Mixed populations	Data reported for paediatric and adult populations (mixed data) is also eligible. Where reported separately, the mixed and separate population data will be extracted.
Interventions/ comparators	In MPS IVA, at least one treatment arm has a licensed dose of ERT e.g. ESA 2mg/kg of body weight given once per week by i.v. infusion over at least 4 hours
Outcomes	Study reports any of the following outcomes of interest:

Characteristic	Inclusion criteria
	Endurance assessments (6MWT, T25FW/MSFC, stair climb test, pinch/grip test, functional dexterity test) Pain Fatigue Psychological assessments Urinary KS Heart function Lung function Survival Audiometry tests Sleep apnoea Corneal clouding Muscle strength HRQoL, MPS HAQ and ADL (listed only)
Study design	RCTs, non-RCTs, single arm/case series SRs/NMAs*
Date limits	Unlimited
Child abstract	Sub-study abstract with unique data that could be reffered to
Publication type	Errata Original articles Technology appraisal documents, if original source not available elsewhere
Languages ¶	Electronic searching will not be limited by English language Any non-English language articles deemed relevant will be discussed with BioMarin to decide on final inclusion. For non-English language articles that are included, Vendor will utilise existing BioMarin support to translate and/or extract relevant information from included articles (if needed +)

Abbreviations: ADL, activities of daily living; ERT, enzyme replacement therapy; ESA, Elosulfase alfa; HRQoL, Health Related Quality of Life; HSCT, hematopoietic stem cell transplantation; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVA, Mucopolysaccharidosis type IVA; MSFC, multiple sclerosis functional composite; 6MWT, 6-minute walk test; NMA, Network meta-analysis; SR, Systematic Review; T25FW, timed 25-foot walk test

* Relevant SRs and meta-analyses will be kept in at 1st pass for cross-referencing/bibliography checking purposes (flagged in Endnote) but will be excluded at 2nd pass. Case reports of interest will be excluded but tagged.

+ Vendor's language capabilities include English, Czech, Danish, French, German, Hungarian, Italian, Polish,
Portuguese and Spanish.

Table 11. Exclusion criteria used for clinical studies (C1 Table)

Characteristic	**Exclusion code & criterion**	**Explanatory notes**
Publication type	e1 pub: Publication type not of interest	e.g. editorials, commentaries, letters, notes, protocol-only articles.
Duplicate	e1 dup: Duplicate/copy	Exact duplicates or copy abstracts, for example where the content is almost identical. If there are discrepancies in the actual data reported, then both will be retained and the discrepancy noted

Child abstract	e1/e2 child: Child abstract or sub-study with no unique data	To be determined at 1st or 2nd pass stage
Languages	e2 lang: Non-English language article agreed between BioMarin and Vendor to be ineligible (+)	Non-English language articles deemed potentially relevant will be discussed with BioMarin to decide on final inclusion.
Population	e1/e2 pop: Population not of interest e.g. non-human data or mixed patient populations (e.g. MPS IVA and other MPS types without MPS IVA data reported separately) <80% of enrolled patients are of the population interest	Where non-human and human data is reported the study will be included if the human data is of relevance Papers where 80% of the population is of interest will be included, or papers where subgroup data with the population of interest are reported separately
Mixed population	e2 mix:	
Interventions / comparators	e1/e2 comp: Treatment in MPS IVA not of interest (e.g. HSCT, gene therapy, symptomatic treatment (physiotherapy / surgery) No comparator of interest or unlicensed dose for treatment of interest (e.g. every other week dosing) without a licensed treatment arm of interest	Treatments of interest in MPS IVA are ERT e.g. ESA, etc.
Sample size	e1 size	<10 patients enrolled (>=10 is includable)
Study design	e1/e2 design: Study design not of interest (e.g. case reports, n=1 before-and-after studies, PK/PD study only, (non-systematic) reviews, observational data, SRs/NMAs	SRs and meta-analyses kept in at 1st pass for cross-referencing purposes but will be excluded at 2nd pass. Case reports of interest will be excluded but tagged.
	Phase 1 only trials	Phase I/II studies reporting phase 2 data are eligible. Phase 1 only studies, or phase I/II studies reporting only the phase 1 data are excluded
	Retrospective studies	
	Case reports	Case series (n>10) may be relevant but not individual case reports
	PK/PD study only	No outcome of interest
	Cluster randomised trials	Individual subjects not randomised
	Non-systematic reviews	Any particularly interesting clinical-type reviews may be noted for discussing in the report. However, in general non-

		systematic reviews will be excluded.
	SRs/MAs/NMAs	Relevant SRs* and MAs are kept in at 1st pass for cross-referencing purposes but will be excluded after 2nd pass, except if MA data not available elsewhere
	Post-hoc pooled analyses	To avoid the same data being included twice. The original trials going in to the pooled analysis, if relevant, will be included.
	Pilot studies	Not robust enough evidence for use
	Economic analyses or budget impact analyses	Clinical outcomes only
	In vitro studies or animal studies	Human in vivo only
Outcomes	e1/e2 out: No outcome of interest	Outcomes not of interest, as they are of little use for clinical management, include urinary GAG tests. Growth and height decreases (due to kyphosis or knee valgus) Immunogenicity will not be collated. While HRQoL outcomes are of interest, these will be captured and extracted in the QoL SR. Those HRQoL values measured will be listed. Papers reporting only incidence or prevalence estimates of MPS IVA will be excluded but tagged.
Date limits	e1/e2 date: No restrictions on original articles. Pre-2018 SRs/meta-analyses excluded	

Abbreviations: ERT, enzyme replacement therapy; ESA, Elosulfase alfa; GAG, glycosaminoglycan; HRQoL, Health Related Quality of Life; HSCT, hematopoietic stem cell transplantation; MPS IVA, Mucopolysaccharidosis type IVA; NMA, Network meta-analysis; SR, Systematic Review;
+ Vendor's language capabilities include English, Czech, Danish, French, German, Hungarian, Italian, Polish, Portuguese and Spanish.
* SRs and meta-analyses will be kept in at 1st pass for cross-referencing/bibliography checking purposes (flagged in Endnote) but will be excluded at 2nd pass. Case reports of interest will be excluded but tagged.

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The electronic database searches identified 650 citations (516 from Medline/Embase, 19 from Medline InProcess/e-publications, 112 from

Cochrane Central Register of Controlled Trials (CENTRAL) and 3 from Cochrane Database of Systematic Reviews (CDSR)). After duplicate removal in Endnote (28 citations), and after first pass (title/abstract) screening (554 exclusions, see Appendix 1, Table 136), 68 papers were screened at second pass. Following full paper review (51 exclusions, Table 137), 17 articles were included from electronic sources (Euctr, 2010, Harmatz et al., 2013, Harmatz et al., 2017, Hendriksz et al., 2018a, Hendriksz et al., 2016a, Hendriksz et al., 2016b, Hendriksz et al., 2015a, Hendriksz et al., 2018b, Hughes et al., 2017, Nagao et al., 2018, Melton et al., 2017, Hendriksz et al., 2013b, Rigoldi et al., 2018, al., 2014, Rigoldi M et al., 2014, EuctrGB, 2009, EuctrIT, 2011b, EuctrIT, 2011a). A further 19 citations were identified via hand-searching (Adam et al., 2019a, Finnigan et al., 2018, Hendriksz et al., 2014c, Adam et al., 2019b, Hughes et al., 2019a, Hughes et al., 2019b, Jones et al., 2015, Mukherjee et al., 2019b, Lampe et al., 2015, Pintos-Morell et al., 2018, BioMarin, 2013, NCT00884949, 2014, NCT01275066, 2014, NCT01415427, 2014, NCT01858103, 2014, NCT01242111, 2015b, NCT01697319, 2016, NCT01515956, 2017, NCT02208661, 2018, NCT03204370, 2019, NCT01966029, 2019). A total of 36 citations were, therefore, included in the SR (

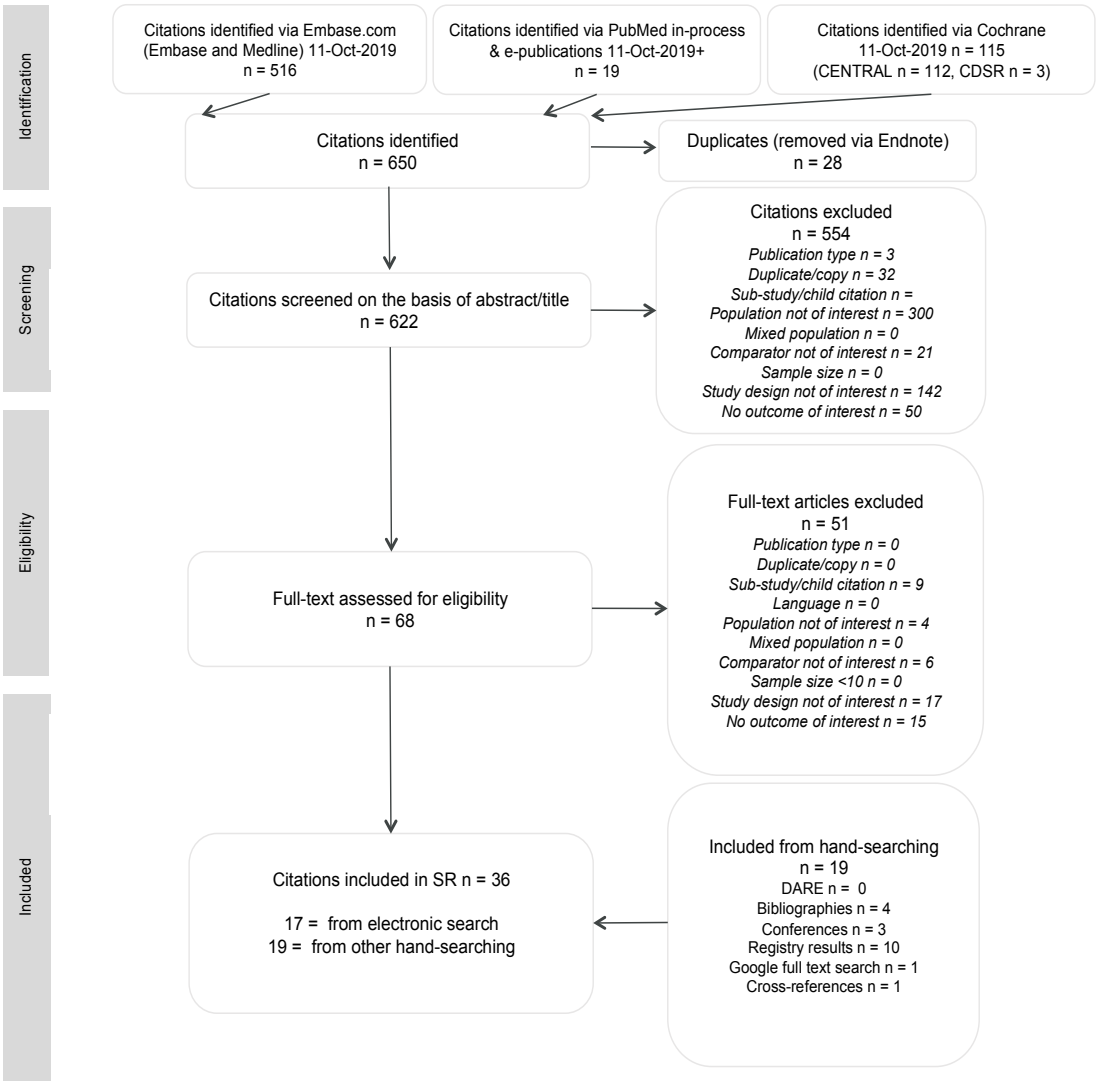
Table 12).

In addition, 10 articles were identified in the new search in November 2020 (see Table 14 below), however two articles (Hendriksz et al., 2015a, Hendriksz et al., 2016b) were already included in the previous SR described above and therefore excluded from the list of new articles (Burton et al., 2020b, Mitchell et al., 2019b, Mitchell et al., 2019c, Mitchell et al., 2020, Moisan et al., 2020, Mukherjee et al., 2020, Ficicioglu et al., 2019b, Tulebayeva et al., 2020, Vashakmadze et al., 2019).

The screening process is summarised in a PRISMA flow diagram (

Figure 8).

Figure 8. PRISMA Flow-chart for study identification and selection of clinical data



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; SR, systematic review
+Search run 11-Oct-2019 and e-alert set up and tracked until 13-Nov-2019

Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Unpublished studies were selected on the same basis as published studies (

Table 12).

Table 12. Selection criteria used for unpublished studies (Table C2)

Inclusion criteria	
Population	MPS IVA (Morquio syndrome) Any age group (children or adults)
Interventions	At least one tx arm has a licensed dose (e.g. ESA 2mg/kg/wk by i.v. infusion over at least 4 hours, *except in the case of natural history studies (where no intervention permitted)*
Outcomes	Study plans to record an outcome of interest: Endurance assessments (6MWT, T25FW/MSFC, 3MSCT, pinch/grip test, functional dexterity test) Pain Fatigue Psychological assessments uKS Heart function Lung function Survival Audiometry tests Sleep apnoea Corneal clouding Muscle strength HRQoL, MPS HAQ and ADL (listed only)
Study design	RCTs, non-RCTs, single arm/case series
Search dates	Unlimited
Exclusion criteria	
Population	Population not MPS IVA, or mixed disease populations
Interventions	Treatment in MPS IVA not of interest (e.g. HSCT, gene therapy, symptomatic treatment (physiotherapy / surgery) No comparator of interest or unlicensed dose for tx of interest (e.g. every other week dosing) without a licensed tx arm of interest, *except in case of natural history studies*
Outcomes	No outcome of interest planned to be measured
Study design	Study design not of interest (e.g. case reports, n=1 before-and-after studies, PK/PD study only, observational data Ph 1 only Case reports Cluster randomised trials Pilot studies Economic analyses or budget impact analyses *In vitro* or animal studies
Search dates	Unrestricted

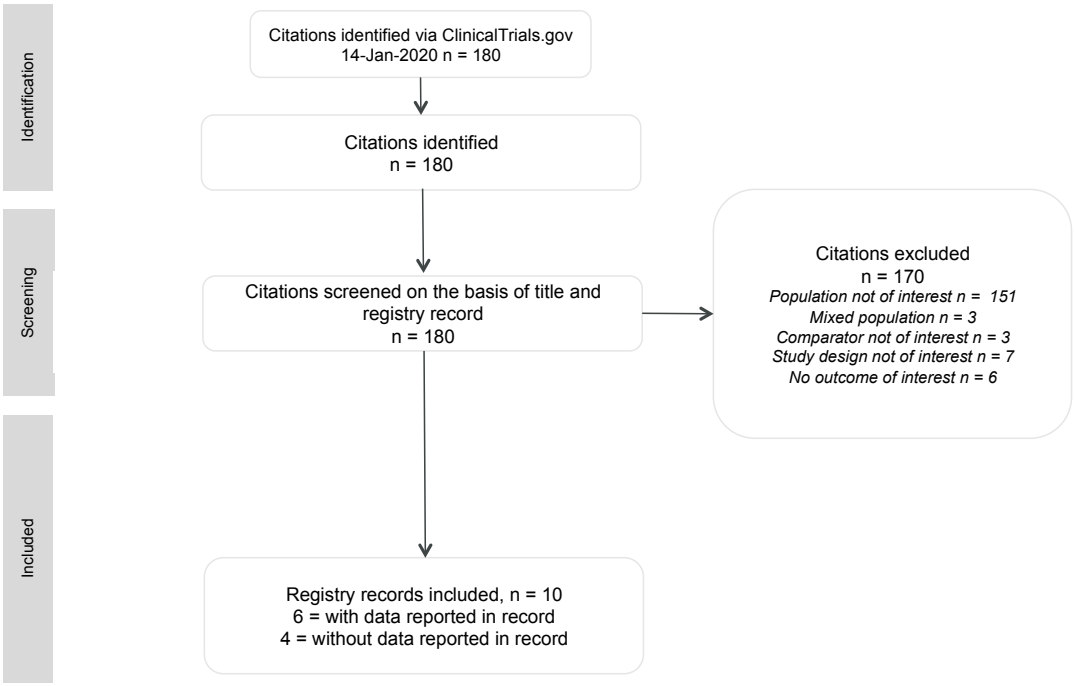
Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; ADL, activities of daily living; ESA, elosulfase alfa; HAQ, health assessment questionnaire; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; MSFC, multiple sclerosis functional composite; PD, pharmacodynamics; Ph, phase; PK, pharmacokinetic; RCT, randomised controlled trial; T25-FW, timed 25 foot walk; uKS, urinary keratan sulphate

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

The ClinicalTrials.gov search retrieved 180 records. These were exported to Excel for screening. 170 citations were excluded for the different reasons mentioned in the below PRISMA flow-chart (Figure 9). 10 records were included from the separate search on Clinicaltrial.gov, which were also identified in the PRISMA above (

Figure 8), 6 of which contained results (Table 13), and 4 of which had no results posted (Table 15). The screening process is summarised in Figure 9.

Figure 9. PRISMA Flow-chart for identification and selection of unpublished studies



9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

The 36 citations (published and unpublished) are provided in two different tables: Table 13Table 13 (32 citations[1]) and Table 15 (4 citations), which summarise all identified published and unpublished studies, respectively. The

[1] Note that Hendriksz 2018a appears twice, as it reports on both MOR-002 and MOR-100

10 citations (published studies) from new searches conducted in November 2020 are provided in Table 14 below.

Table 13 citations include journal publications and NIH registry entries for those studies that provide additional methodological detail or additional results data in the registry entry.

Table 14. List of new relevant published studies (November 2020 SR update)

Author, Year	Study name (acronym)	Design / population	Intervention(s)	Comparator(s)
Ficicioglu, Benedict et al. 2019	Sibling control study	3 siblings with MPS IVA	ESA 2.0 mg/kg qw	N/A
Mitchell, Iannuzzi et al. 2019	Clinical characteristics of French-Canadians with MPS IVA	Longitudinal cohort study of patients in Quebec, Canada, with MPS IVA	ESA 2.0 mg/kg qw	N/A
Vashakmadze, Jourkova et al. 2019	Cardiac disease in patients with mucopolysaccharidoses in Russia	Observational study of cardiac disease in patients with MPS in Russia	ERT	N/A
Burton, Guffon et al. 2020	MARS	MARS data	ESA 2.0 mg/kg qw	N/A
Mitchell, Ramaswami et al. 2020	MARS	MARS data	ESA 2.0 mg/kg qw	N/A
Moisan, Iannuzzi et al. 2020	Clinical characteristics of patients from Quebec, Canada, with MPS IVA	Longitudinal observational study	ESA 2.0 mg/kg qw	N/A
Mukherjee, Davison et al. 2020	MAA	MAA data, ENG	ESA 2.0 mg/kg qw	N/A
Tulebayeva et al. 2020	Respiratory dysfunction in children and adolescents with mucopolysaccharidosis types I, II, IVA, and VI	Prospective study of respiratory system in patients with MPS	ERT	N/A

Table 15 citations are all NIH registry records for studies for which there not yet any journal publications or any results reported in the registry record.

Table 13. List of relevant published studies

Author, Year	Study name (acronym)	Design / population	Intervention(s)	Comparator(s)
Hendriksz, 2018 (EuctrGB, 2009, NCT00884949, 2014, Hendriksz et al., 2018a, CJ et al., 2013)	MOR-002	Ph 1/2 OL, dose-escalation study, pts 5-18 yrs	ESA (Dose-escalation across 36 wks, divided into 3 consecutive 12-wk intervals, at doses of 0.1, 1.0, and 2.0 mg/kg qw, followed by continuation period 36-48 wks 1.0 mg/kg qw)	N/A
Hendriksz, 2018 (Hendriksz et al., 2018a, NCT01242111, 2015a, Euctr, 2010)	MOR-100	OLE of MOR-002, pts 5-18 yrs	ESA 2.0 mg/kg qw	N/A
Hendriksz, 2014 (NCT01275066, 2014, EuctrIT, 2011b, Hendriksz et al., 2014b, Hendriksz et al., 2015b, Melton et al., 2017)	MOR-004	Ph 3 DB RCT (PLA-controlled) in pts ≥5 yrs with 6MWT distance between 30m and 325m	ESA 2.0 mg/kg qw ESA 2.0 mg/kg qow	PLA
Hendriksz, 2016 (NCT01415427, 2014, EuctrIT, 2011a, Hendriksz et al., 2016a, Hendriksz et al., 2016c, Hughes et al., 2017)	MOR-005	Ph 3 EXT, DB then OLE, pts ≥5 yrs	DB: ESA 2.0 mg/kg qw ESA 2.0 mg/kg qow OL: ESA 2.0 mg/kg qw	N/A
Harmatz et al, 2017 (NCT01697319, 2016, Harmatz et al., 2017)	MOR-006	Ph 2 OL study in pts ≥5 yrs with limited ambulation (unable to walk >30m in 6MWT)	ESA 2.0 mg/kg qw	N/A
Jones et al, 2015 (NCT01515956, 2017, Jones et al., 2015)	MOR-007	Ph 2 OL study in pts <5 yrs of age	ESA 2.0 mg/kg qw	N/A
Adam, 2019 (Adam et al., 2019a, Hughes et al., 2019a)	MAA	MAA data, ENG	ESA	N/A
Finnigan et al., 2018	Home infusion study	Home infusion study, Manchester UK, pts 4-16 yrs	ESA 2.0 mg/kg qw	N/A

Author, Year	Study name (acronym)	Design / population	Intervention(s)	Comparator(s)
(Finnigan et al., 2018)				
Harmatz et al., 2013 (P. et al., 2013)	Safety analysis	Long-term safety analysis (>48 wks exposure)	ESA 2.0 mg/kg qw	N/A
Hendriksz et al., 2014 (Hendriksz et al., 2014c)	PRO survey	PRO survey in caregivers to MPS IVA pts	N/A	N/A
Mukherjee et al., 2019 (Mukherjee et al., 2019a)	MAA	MAA data, ENG	ESA	N/A
Nagao et al., 2018 (Nagao et al., 2018)	NR	Hearing study, 13 MPS IVA and 1 MPS IVB; aged 12-38 yrs	NR	N/A
BioMarin Pharmaceuticals, 2013 (BioMarin, 2013)	Report	Briefing document for Advisory Committee	ESA	N/A
Pintos-Morell et al., 2018 (Pintos-Morell et al., 2018)	ESP EAP	ESP EAP, 7-17 yrs	ESA 2.0 mg/kg qw	N/A
Lampe et al., 2015 (Lampe et al., 2015)	DEU PRO study	DEU PRO study, 14 adults aged 18-54 yrs and 10 children aged 10-17 yrs	NR	N/A
Rigoldi et al., 2014 (Rigoldi M et al., 2014)	NR	IQ study	NR	N/A

Abbreviations: 6MWT, 6-minute walk test; DB, double-blind; DEU, Germany; EAP, expanded access program; ENG, England; ESA, elosulfase alfa; ESP, Spain; EXT, extension; IQ, intelligence quotient; MAA, market access agreement; N/A, not applicable; NR, not reported; OL, open-label; OLE, open-label extension; ph, phase; PLA, placebo; PRO, patient-reported outcomes; pts, patients; qw, per week; RCT, randomised controlled trial; UK, United Kingdom; USA, United States of America; wks, weeks

Table 14. List of new relevant published studies (November 2020 SR update)

Author, Year	Study name (acronym)	Design / population	Intervention(s)	Comparator(s)
Ficicioglu, Benedict et al. 2019	Sibling control study	3 siblings with MPS IVA	ESA 2.0 mg/kg qw	N/A

Author, Year	Study name (acronym)	Design / population	Intervention(s)	Comparator(s)
Mitchell, Iannuzzi et al. 2019	Clinical characteristics of French-Canadians with MPS IVA	Longitudinal cohort study of patients in Quebec, Canada, with MPS IVA	ESA 2.0 mg/kg qw	N/A
Vashakmadze, Jourkova et al. 2019	Cardiac disease in patients with mucopolysaccharidoses in Russia	Observational study of cardiac disease in patients with MPS in Russia	ERT	N/A
Burton, Guffon et al. 2020	MARS	MARS data	ESA 2.0 mg/kg qw	N/A
Mitchell, Ramaswami et al. 2020	MARS	MARS data	ESA 2.0 mg/kg qw	N/A
Moisan, Iannuzzi et al. 2020	Clinical characteristics of patients from Quebec, Canada, with MPS IVA	Longitudinal observational study	ESA 2.0 mg/kg qw	N/A
Mukherjee, Davison et al. 2020	MAA	MAA data, ENG	ESA 2.0 mg/kg qw	N/A
Tulebayeva et al. 2020	Respiratory dysfunction in children and adolescents with mucopolysaccharidosis types I, II, IVA, and VI	Prospective study of respiratory system in patients with MPS	ERT	N/A

Table 15. List of relevant unpublished studies

Author, Year	Study name (acronym)	Design / population	Intervention(s)	Comparator(s)
NCT01858103, 2014d	110-503	USA EAP	ESA 2.0 mg/kg qw	N/A
NCT01966029, 2019b	110-502 MOR-AUS	Ph 3B in AUS pts	ESA 2.0 mg/kg qw	N/A
NCT02208661, 2018	MAPLE	Psychological and QoL study before/after ESA in adult pts	NR	N/A
NCT03204370, 2019a	BMRN58492	Natural history study in non-classical (less severe) pts 18-55 yrs	ESA 1.0 mg/ml i.v. solution	N/A

Abbreviations: AUS, Australia; EAP, Expanded Access Program; ESA, elosulfase alfa; N/A, non-applicable; Ph, phase; QoL, quality-of-life; qw, per week; USA, United States of America; yrs, years

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

Burton et al., 2015 (Burton et al., 2015) was excluded from the SR because MOR-008 was a pilot study. Results of MOR-008 are presented in Section 9.6.1.1 below.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

Study design and methods are summarised in Table 16 and Table 23 (RCTs) and in Tables 17-29 (non-RCTs and single-arm studies). The following table provides quick access to the relevant studies:

Study	Cross-reference
MOR-004 and MOR-005	Table 16
MOR-002 and MOR-100	Table 17
MOR-006	Table 19
MOR-007	Table 21
Observational studies	Table 26, Table 27, Table 28, Table 29
Clinical trial of interest excluded in the systematic literature review (pilot study)	
MOR-008 (Burton et al. 2015)	Table 23
Real-world evidence studies	
MARS	Study design
Managed Access Agreement	Table 24

MOR-004 and MOR-005

A summary of the methodology is presented in Table 16. Patient disposition and baseline characteristics is described following the above-mentioned tables.

Table 16. Summary of methodology of randomised controlled trial and its extension: MOR-004/MOR-005

Study name (acronym)	MOR-004	MOR-005
Author, Year (main)	Hendriksz, Burton et al., 2014b	Hendriksz, Parini et al.,, 2016c
Design / population	Ph 3 DB RCT (PLA-controlled) in pts ≥5 yrs with 6MWT distance between 30m and 325m	Ph 3 EXT, DB then OLE, pts ≥5 yrs
Intervention(s)	ESA 2.0 mg/kg qw ESA 2.0 mg/kg qow	DB (part 1): ESA 2.0 mg/kg qw ESA 2.0 mg/kg qow OLE (part 2): ESA 2.0 mg/kg qw
Comparator(s)	PLA	N/A
Population	≥ 5 yrs, confirmed Morquio A (documented reduced GALNS or genetic testing)	≥ 5 yrs, confirmed MPS IVA (documented reduced GALNS or genetic testing)
Objectives	To assess the efficacy and safety of enzyme replacement therapy with ESA in pts with MPS IVA	To present MPS-HAQ outcomes over 1 and 2 years in the MOR-004/005 trial and to compare these with MPS-HAQ outcomes over a similar time period in a comparable untreated cohort of Morquio A patients from the MorCAP natural history study
Location/Study setting	International, 17 countries (USA, ARG, BRA, CAN, COL, DNK, FRA, DEU, ITA, JPN, KOR, NLD, POR, QAT, SAU, TWN, UK)	International, 20 countries (USA, ARG, BRA, CAN, COL, DNK, FRA, DEU, ITA, JPN, KOR, NLD, NOR, POR, QAT, SAU, ESP, TWN, TUR, UK)
Study design	Ph 3, DB RCT, parallel-arm	Ph 3 EXT study: DB RCT followed by OLE
Duration of study	24 wks	120 wks
Sample size	Randomised 177 mITT=176 1 pt was randomised but not treated and was excluded because the diagnosis was not confirmed	Part 1: 173 Part 2: 169
Inclusion criteria	≥5 yrs with 6MWT distance between 30m and 325m, documented clinical diagnosis of MPS IVA	Completed MOR-004
Exclusion criteria	6MWT <30m, 6MWT >325m, HSCT or ESA-treated patients, surgery within 3 months of enrolment or planned in 24 weeks	Prior investigational product or device (other than ESA in MOR-004) within 30 days of BL, previous ESA study other than MOR-004, concurrent disease that would interfere with participation or be a safety risk (e.g.

Study name (acronym)	MOR-004	MOR-005
	of study, symptomatic cervical spine instablity, significant spinal cord compression, severe cardiac disease	symptomatic cervical spine instability, clinically significant spinal cord compression, severe cardiac disease)
Method of randomisation	NR but stratified by screening 6MWT category (<=200 and >200 m) and age group (5–11, 12–18, >=19 yrs old)	NR, re-randomisation not stratified
Method of blinding	Described as double-blind. Statement "Patients, investigators and site personnel were blinded to treatment assignment throughout the study and until the final analysis was complete". Also, patients randomised to the arm with (active) treatment every other week were given placebo infusions on alternative weeks to mask active drug weeks.	Described as DB. Further, masking described as quadruple: participant, care provider, investigator, outcomes assessor
Treatment arms (NITT/ NmITT)	ESA 2mg/kg/week (58) ESA 2mg/kg qow (59) PLA (59)	ESA 2mg/kg/week (56) ESA 2mg/kg qow (59) PLA-QW (29) PLA-QOW (29)
Baseline differences	Tx arms balanced at baseline	Randomisation on entry to MOR-005 was not stratified and a chance imbalance occurred in MOR-005 BL characteristics (age and endurance measures)
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	24 wks, tx compliance high, almost all pts completed study, after which they could enrol in MOR-005	120 wks (including 24 wks of MOR-004)
Statistical tests	ANCOVA model with BL 6MWT category (<=200, >200m) and age group (5-11, 12-19, >=19 yrs) as covariates. For 2ry endpoints, due to multiplicity, step-down testing procedure used (3MSCT had to show sig result first and only then could uKS be declared sig. Hochberg method for multiplicity adjustment used for the two tx comparisons with PLA. Missing data was addressed using multiple imputation for 1ry, 2ry and respiratory function endpoings (joint normal distribution)	Descriptive stats. Repeated measures ANCOVA model (incl. tx, time point, tx and time point interaction, BL age stratum (5-11, 12-18, >=19 yrs), BL 6MWT distance stratum (<=200m, >200m), and BL measurement (for 3MSCT and uKS) as factors) used to compare LS mean changes from BL at Yr 1 and Yr 2 between MOR-005 and MorCAP populations. Only pts continually on ESA 2.0mg/kg/wk were compared to MorCAP.

Study name (acronym)	MOR-004	MOR-005
Primary outcomes (including scoring methods and timings of assessments)	6MWT change from BL at wk 24 for each ESA group vs PLA	6MWT, 24 wks, 36 wks, 72 wks, 120 wks
Secondary outcomes (including scoring methods and timings of assessments)	3MSCT change from BL at wk 24 Norm uKS change from BL at wk 24	3MSCT, 24 wks, 36 wks, 72 wks, 120 wks uKS 120 wks

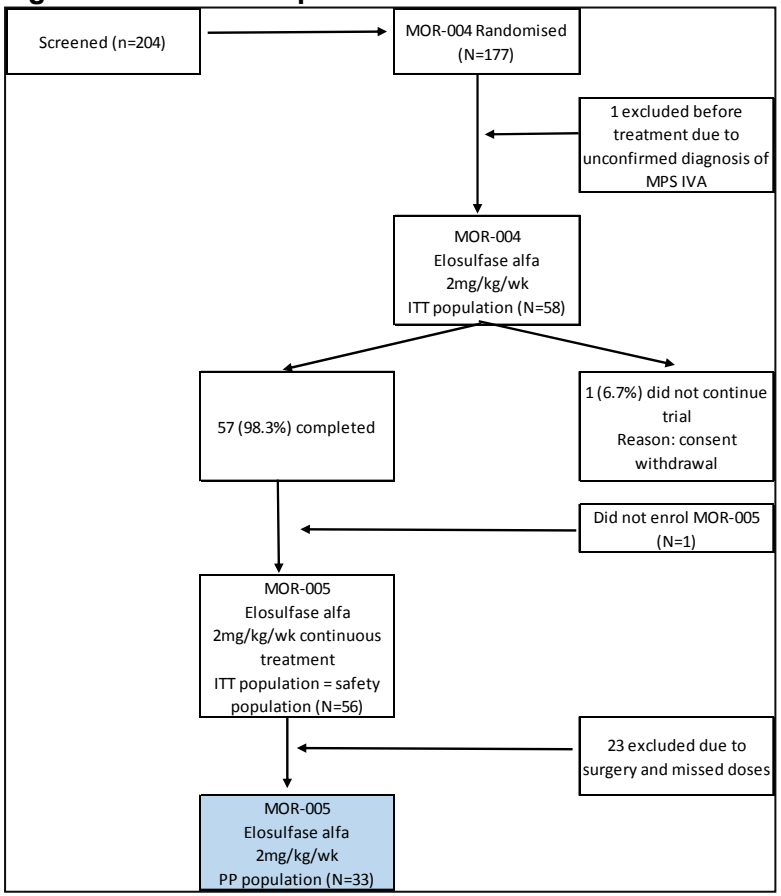
Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; ANCOVA, analysis of covariance; ARG, Argentina; BL, baseline; BRA, Brazil; CAN, Canada; COL, Columbia; DB, double-blind; DEU, Germany; DNK, Denmark; ESA, elosulfase alfa; FRA, France; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; m, metre; ITA, Italy; JPN, Japan; KOR, South Korea; NLD, The Netherlands; Ph, phase; PLA, placebo; POR, Portugal; pts, patients; QAT, Qatar; qow, every other week; qw, weekly; RCT, randomised controlled trial; SAU, Saudi Arabia; sig, significant; TWN, Taiwan; tx, treatment; uKS, urinary keratan sulphate; UK, United Kingdom; USA, United States of America; wk, week; wks, weeks; yrs, years

Patient disposition and baseline characteristics at baseline

The patient disposition for MOR-004/MOR-005 can be found in

Figure 10. The ITT population is confounded by surgery even for the QW-QW population and the other populations are confounded by the times of transition to the indicated dose and as such not representing long term use of elosulfase alfa. The relevant population of MOR-005 are those patients who are treated with the indicated dose of elosulfase alfa of 2.0 mg/kg/week, retained acceptable compliance of >80% and have not undergone surgery, described as the modified per protocol (MPP).

Figure 10. Patient disposition in MOR-004/MOR-005



MOR-002 and MOR-100

Summary of the methodology is presented in Table 17. Following, the patient disposition and baseline characteristics are described.

Table 17. Summary of methodology of clinical trial studies: MOR-002 and MOR-100

Study name (acronym)	MOR-002	MOR-100
Author, Year	Hendriksz, Santra et al.2018a	Hendriksz,Santra et al., 2018a
Design / population	Ph 1/2 OL, dose-escalation study, pts 5-18 yrs	OLE of MOR-002, pts 5-18 yrs
Intervention(s)	ESA (Dose-escalation across 36 wks, divided into 3 consecutive 12-wk intervals, at doses of 0.1, 1.0, and 2.0 mg/kg qw) + (Continuation period 36-48 wks 1.0 mg/kg qw)	ESA 2.0 mg/kg qw
Comparator(s)	N/A	N/A
Population	5-18 yrs confirmed MPS IVA (documented reduced GALNS enzyme activity or genetic testing)	5-18 yrs confirmed MPS IVA (documented reduced GALNS enzyme activity or genetic testing)
Objectives	To assess the safety and tolerability of escalating doses of ESA	To evaluate the safety of weekly infusions of ESA
Location/Study setting	UK	UK
Study design	Multicenter, open-label, phase 1/2	Multicenter, open-label, phase 1/2
Duration of study	Dose escalation 36 wks Continuation 36-48 wks	192 wks
Sample size	20	20
Inclusion criteria	Documented history of reduced GALNS activity relative to the normal range of the laboratory performing the assay, or documented result of molecular genetic testing confirming diagnosis of MPS IVA Between 5-18 yrs of age, inclusive	Must have enrolled in a prior BioMarin sponsored clinical study of BMN 110
Exclusion criteria	Previous HSCT Known hypersensitivity to ESA or its excipients	Use of any investigational product (other than BMN 110 in a prior clinical study) or investigational medical device

Study name (acronym)	MOR-002	MOR-100
	Use of any investigational product or investigational medical device within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments Concurrent disease or condition that would interfere with study participation or safety, including, but not limited to, symptomatic cervical spine instability Any condition that, in the view of the PI, places the subject at high risk of poor treatment compliance or of not completing the study	within 30 days prior to Baseline, or requirement for any investigational agent prior to completion of all scheduled study assessments. Concurrent disease or condition, including but not limited to symptomatic cervical spine instability, clinically significant spinal cord compression, or severe cardiac disease that would interfere with study participation or safety as determined by the Investigator. Any condition that, in the view of the Investigator, places pt at high risk of poor tx compliance or of not completing the study. Were enrolled in MOR-004 (pts from MOR-004 eligible to participate in a separate, appropriately designed, EXT study).
Method of randomisation	N/A	N/A
Method of blinding	N/A	N/A
Treatment arms (NITT/ NmITT)	ESA (Dose-escalation across 36 wks, divided into 3 consecutive 12-wk intervals, at doses of 0.1, 1.0, and 2.0 mg/kg qw) + (Continuation period 36-48 wks 1.0 mg/kg qw) (20)	ESA 2mg/kg/week (20)
Baseline differences	One four-year-old pt was 6 wks younger than the 5-yr minimum age and was granted an exemption. Pts exhibited a wide range of functional impairment and organ system involvement due to the heterogeneity of the disease.	Pts exhibited a wide range of functional impairment and organ system involvement due to the heterogeneity of the disease
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	Up to 84 wks	Up to 240 wks (entire study period)
Statistical tests	Descriptive statistics were used to summarise outcomes at each dose level in MOR-002	For a better understanding of outcomes relative to tx duration, and to account for missing data in the EXT study, a post hoc analysis was performed using recorded assessment dates to determine actual tx duration in 3-month increments. A mixed-model analysis, including repeated measures for pts and mths, was used to estimate LS assessment outcomes by tx duration

Study name (acronym)	MOR-002	MOR-100
Primary outcomes (including scoring methods and timings of assessments)	Subject incidence of treatment-emergent AEs, entire study through wk 84	AEs, up to 240 wks
Secondary outcomes (including scoring methods and timings of assessments)	Change from BL in 6MWT, 3MSCT, BL to wks 12, 24, 36, 48, 72 Percent change from BL in norm uKS, MVV, FVC, BL to wks 12, 24, 36, 72	Change from BL in 6MWT and 3MSCT every 24 wks for up to 192 wks. Percent change from BL in uKS levels every 24 wks for up to 168 wks. Percent change from BL in MVV and FVC every 24 wks for up to 192 wks.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; AE, adverse event; BL, baseline; ESA, elosulfase alfa; EXT, extension; FVC, forced vital capacity; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; MVV, maximum ventilation volume; OL, open-label; OLE, open-label extension; PI, principal investigator; uKS, urinary keratan sulphate; qw, weekly; UK, United Kingdom; wks, weeks

Patient disposition and baseline characteristics at baseline

During the 0.1 mg/kg dosing phase, 1 patient discontinued due to a type I hypersensitivity adverse event (AE), and that patient's sibling voluntarily discontinued in the absence of AEs. An additional patient discontinued due to recurrent infusion reactions during the 1.0 mg/kg continuation phase. The remaining 17 patients completed MOR-002 and enrolled in MOR-100, an open-label, long-term extension study that further evaluated safety and clinical outcomes with elosulfase alfa administered at 2.0 mg/kg qw. The baseline characteristics of the patients in MOR-002 and 100 are shown in

Table 18 below.

Table 18. Baseline characteristics of MOR-002/100

	MOR-002 (n=20)	MOR-100 (n=17)
Age at enrolment Mean (SD) Median Range	 8.4 (2.90) 7.9 4,16	 8.1 (2.78) 7.5 4,16
Sex (%) Female Male	 8 (40) 12 (60)	 8 (47.1) 9 (52.9)
Baseline endurance 6MWT mean (SD) 3MSCT mean (SD)	 266.0 (137.9) 38.9 (25.39)	 N/A N/A

MOR-006

Summary of the methodology is presented in Table 19. Following, the patient disposition and baseline characteristics are described.

Table 19. Summary of methodology of observational study: MOR-006

Study name (acronym)	MOR-006
Author, Year	Harmatz et al., 2017
Design / population	Ph 2 OL study in pts ≥5 yrs with limited ambulation (unable to walk >30m in 6MWT)
Intervention(s)	ESA 2.0 mg/kg qw
Comparator(s)	N/A
Population	≥ 5 yrs, unable to walk >30m in 6MWT, confirmed Morquio A (based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing)
Objectives	To assess efficacy and safety of ESA ERT in Morquio A patients aged ≥5 years unable to walk ≥30 meters in the 6-min walk test
Location/Study setting	INT, (USA, DEU, UK)
Study design	Ph 2, OL, Multinational
Duration of study	144 wks Primary tx phase = 48 wks EXT phase = 96 wks
Sample size	16
Inclusion criteria	Confirmed diagnosis of Morquio A syndrome, age ≥5 years, inability to walk ≥30m in 6MWT at screening visit Documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA.
Exclusion criteria	Able to walk farther than a specified distance as assessed by 6MWT. Previous HSCT.

Study name (acronym)	MOR-006
	Previous tx with ESA. Known hypersensitivity to any of the components of ESA. Had major surgery within 3 months prior to study entry or is planning to have a major surgery during the first 24 wks of study. Used any other investigational product or investigational medical device within 30 days prior to Screening Visit or requires any investigational agent prior to completion of all scheduled study assessments. Has a concurrent disease or condition, including but not limited to symptomatic cervical spine instability or severe cardiac disease or complete paralysis due to a spinal cord injury (defined as an inability to move arms and legs), that would interfere with study participation or safety as determined by Investigator.
Method of randomisation	N/A
Method of blinding	N/A
Treatment arms (NITT/ NmITT)	ESA 2.0 mg/kg/week mITT n=15
Baseline differences	MPP population consisted of 10 pts Only three pts were able to walk on their feet at BL, one of them with a walking device. One pt (pt 8) had an inclusion/exclusion waiver granted, as he walked slightly more than 30m (31.7 m) on 6MWT at BL
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	144 wks including extension phase
Statistical tests	As several pts from ITT population were not compliant with the protocol or did not remain in the study for 48 wks due to logistical issues, acute disease related to Morquio A, or adverse reactions to study drug, descriptive statistics of efficacy measured from BL through wk 48 are presented for MPP population.
Primary outcomes (including scoring methods and timings of assessments)	Percent change from BL in speed (FDT), up to 96 wks Change from BL in strength (GPT), up to 96 wks Percent change from BL in speed (Timed 25FWT), up to 96 wks
Secondary outcomes (including scoring methods and timings of assessments)	Percent change from BL in norm uKS, up to 96 wks

Abbreviations: 6MWT, 6-minute walk test; BL, baseline; DEU, Germany; ESA, elosulfase alfa; EXT, extension; FDT, functional dexterity test; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; GPT, grip and pinch test; HSCT, haematopoietic stem cell transplantation; INT, international; ITT, intention-to-treat; m, metres; mITT, modified intention-to-treat; OL, open-label; Ph, phase; pts, patients; qw, weekly; UK, United Kingdom; USA, United States of America; yrs, years

Patient disposition and baseline characteristics at baseline

Of the 16 patients enrolled in MOR-006, 15 received at least one dose of study drug. The patient who did not receive any study treatment could not physically commit to the necessary weekly travel. Of the 15 patients treated, 12 completed at least 48 weeks of study treatment. Two patients discontinued

ERT at 4 weeks due to grade 3 drug-related AEs (infusion related reaction and hypersensitivity). Of the 12 patients completing 48 weeks of study treatment, two missed more than 20% of their scheduled infusions. Thus, the final efficacy population consisted of ten patients, whose demographics and baseline characteristics are shown in Table 20. All patients of the MPP population had very short stature (90–110 cm) and severe skeletal and joint abnormalities and most had restrictive and/or obstructive lung disease. All patients had a history of multiple surgeries, including adenoidectomy/tonsillectomy, spinal cord decompression/fusion surgery, hip or knee surgery, or tracheotomy.

Table 20. Demographics and Baseline Characteristics of Patients Included in the Modified Per Protocol (MPP) Population

Patient	Age at baseline	Sex	FDT pegs/min	Method of ambulation in T25FW	T25FW speed feet/min
1	12.8	M	4.5	Crawling	6.9
2	18.9	M	18.5	Knee walking	66.7
3	17.3	F	16.3	Crawling using arms only	0.6
4	29.6	M	11.4	Physically unable	NA
5	12.6	F	31.0	Physically unable	NA
6	9.8	M	4.0	Physically unable	NA
7	13.9	F	Physically unable	Physically unable	NA
8	42.2	M	31.0	Unassisted walking	88.2
9	31.0	M	13.5	Unassisted walking	21.4
10	24.5	F	24.0	Walking frame	44.8
Mean (SE)	21.3 (3.3)		17.1 (3.4)		38.1 (14.2)

MOR-007

Summary of the methodology is presented in Table 21. Following, the patient disposition and baseline characteristics are described.

Table 21. Summary of methodology of observational study: MOR-007

Study name (acronym)	MOR-007
Author, Year	Jones et al., 2015
Design / population	Ph 2 OL study in pts <5 yrs of age
Intervention(s)	ESA 2.0 mg/kg qw
Comparator(s)	N/A
Population	< 5 yrs, confirmed Morquio A (documented reduced GALNS or genetic testing)
Objectives	To evaluate safety and impact on uKS levels and growth velocity in younger pts
Location/Study setting	INT
Study design	Ph 2, OL, multinational, followed by EXT
Duration of study	Primary tx phase = 52 wks EXT = 156 wks
Sample size	15
Inclusion criteria	<5 yrs of age at first infusion. Documented clinical diagnosis of Morquio A syndrome based on reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming the diagnosis.
Exclusion criteria	>=5 yrs, previous HSCT or ESA, major surgery within 3 months of enrolment or planned in initial tx period, symptomatic cervical spine instability, clinically significant spinal cord compression, severe cardiac disease
Method of randomisation	N/A
Method of blinding	N/A
Treatment arms (NITT/ NmITT)	ESA 2mg/kg/week (15)
Baseline differences	NR
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	Primary tx phase = 52 wks EXT = 156 wks
Statistical tests	Descriptive statistical summaries of continuous variables: mean, SD, median, and range. Descriptive summaries of categorical variables included sample size and percent.
Primary outcomes (including scoring methods and timings of assessments)	Number of participants experiencing AEs, up to 52 wks
Secondary outcomes (including scoring methods and timings of assessments)	Percent change from BL to wk 52 in uKS measures Change from BL in norm Growth Rate Z-Scores, up to wk 52

Abbreviations: AE, adverse event; BL, baseline; ESA, elosulfase alfa; EXT, extension; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; HSCT, haematopoietic stem cell transplantation; INT, international; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT

population; OL, open-label; Ph, phase; pts, patients; qw, weekly; tx, treatment; uKS, urinary keratan sulphate; wks, weeks; yrs, years

Baseline characteristics at baseline

Fifteen patients aged 9 months to 4.9 years were enrolled in the study. All patients completed the primary treatment phase, and none permanently discontinued elosulfase alfa. Demographic and baseline data are presented in Table 22.

Table 22. Demographics and baseline characteristics of MOR-007

	Elosulfase 2.0mg/kg/wk (N=15)
Age at enrolment Mean (SD) Median Min, Max	 3.1 (1.3) 3.1 0.8, 4.9
Sex (%) Female Male	 7 (46.7) 8 (53.3)
Normalised uKS[a] (ug/mg) Mean (SD) Median Min, Max	 35.9 (12.3) 35.4 18.8, 56.5
Length (cm) Mean (SD) Median Min, Max	 90.1 (9.3) 89.6 75.8, 113.0
Standing heightb (cm) Mean (SD) Median Min, Max	 88.9 (9.0) 90.0 72.3, 109.2

[a] Normalized urine keratan sulfate (uKS) is calculated as urine KS divided by urine creatinine. Normalized uKS level in healthy controls aged 0-6 y range between 0.42 and 5.7 µg/mg creatinine (12).
b Height was not obtained for two of the patients who were < 2 y of age.

MOR-008 (pilot study, excluded from SR)

Summary of study design

MOR-008 is a multinational, multicentre, phase 2, two-arm, randomised, double-blind, pilot study evaluating the effect of elosulfase alfa treatment for 52 weeks on exercise capacity, as assessed by CPET and measures of endurance.

Briefly, after a 3-week screening period, 25 patients aged ≥7 years able to walk >200 m in the 6MWT and to perform an exercise test were randomised

in a double-blind fashion to elosulfase alfa 2.0 mg/kg/week (N=15) or 4.0mg/kg/week (N=10) for 27 weeks. Randomization was stratified by cohort: CPET (N=15) and no CPET (N=10). The primary endpoint was safety and tolerability of elosulfase alfa over 27 weeks. Secondary endpoints were effect on endurance (6MWT, 3MSCT), exercise capacity, respiratory function, muscle strength, cardiac function, pain, and urinary KS level. Patients who completed the primary treatment phase were enrolled in the extension, during which all patients continued on the same dose of elosulfase alfa up to 52 weeks.

Patient characteristics

Twenty-five patients were enrolled (15 randomized to 2.0 mg/kg/week and 10 to 4.0 mg/kg/week). All 25 patients (median age 12 years; range 8–21 years) completed the primary treatment phase and were enrolled in and completed 52 weeks of the extension study. CPET was assessed only in the first 15 patients enrolled in the study. As such the results presented below are only for these 15 patients. Table 23 shows baseline characteristics for the 15 patients included in the CPET analysis.

Table 23. Demographics and baseline characteristics of patients included in the cardiopulmonary exercise test (CPET) analysis (modified intent-to-treat population)

	Total Patients (N=15)
Age at enrolment in years Median (range)	 12 (8, 21)
Sex, N (%) Female Male	 10 (66) 5 (34)
Height in cm Median (range)	 106.5 (85, 167)
Weight in Kg Median (range)	 26.4 (12, 54)
6MWT in m Median (range)	 331 (273, 466)
3MSCT in stairs/min Median (range)	 58 (28, 87)

Managed Access Agreement (MAA) in England

Patients diagnosed with MPS IVA in England are eligible for treatment with elosulfase alfa if they meet specific starting criteria, as specified in the MAA. Patients aged ≥5 years can only start treatment once a full set of baseline assessments is obtained. All patients or their parents provided written, signed informed consent to participate in the study.

As part of the MAA programme, patients were monitored on an annual basis and have to cease therapy if they are non-compliant (miss ≥3 infusions in any 14-month period without medical reasons), are unable to tolerate infusions due to infusion-related reactions that cannot be controlled, or fail to meet four of the five criteria outlined in

Table 9. These criteria were based largely on clinical trial outcomes but agreed upon by a group of clinical experts and commissioners.

Summary of the methodology is presented in Table 24.

Table 24. Summary of methodology of Managed Access Agreement (MAA) in England

Study name (acronym)	MAA	
Author, Year	Adam et al., 2019a	Mukherjee et al., 2019
Design / population	MAA data, England	MAA data, England
Intervention(s)	ESA 2.0mg/kg/wk	ESA 2.0mg/kg/wk
Comparator(s)	N/A	N/A
Population	MPS IVA pts receiving tx under MAA	MPS IVA pts receiving tx under MAA
Objectives	Authors presented PROs from pts on ESA under MAA	Authors reported clinical outcomes for long term use with ESA from MAA
Location/Study setting	ENG	ENG
Study design	MAA pts follow-up	MAA pts follow-up
Duration of study	24 mths (data as of March 2018)	24 mths (Data as of Jan 2019)
Sample size	36	47
Inclusion criteria	Pts in MAA receiving ERT ≥2 yrs	Pts in MAA receiving ERT ≥2 yrs
Exclusion criteria	NR	NR
Method of randomisation	N/A	N/A
Method of blinding	N/A	N/A
Treatment arms (NITT/ NmITT)	NR	NR
Baseline differences	26 initiated tx in clinical trials, tx duration mean (SD) 7 (1.4) yrs 10 initiated treatment in MAA, tx duration mean (SD) 2.1 (0.3) yrs	26 pts initiated ERT in clinical trials, ages 9.86–47.83 yrs, ERT duration mean (SD) 7.5 (1.9) yrs 21 pts initiated ERT in MAA, ages 6.01–58 yrs, ERT duration mean (SD) 2.7 (0.2) yrs

Study name (acronym)		MAA
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	24 mths	24 mths but background also stated pts had to annually demonstrate an improvement or stabilisation in at least 4 of 5 clinical and PROs
Statistical tests	NR	NR
Primary outcomes (including scoring methods and timings of assessments)	Mean change from BL - 24 mths: EQ-5D-5L, MPS-HAQ CD, APPT, BPI Mean change from BL - 20 mths: BDI	Mean change from BL - 24 mths in 6MWT, FVC, FEV1, uKS, EF
Secondary outcomes (including scoring methods and timings of assessments)	NR	NR

Abbreviations: 6MWT, 6-minute walk test; APPT, Adolescent and Pediatric Pain Tool; BDI, Beck depression inventory; BL, baseline; BPI, brief pain inventory; CD, caregiver domain; EF, ejection fraction; ENG, England; EQ-5D-5L, EuroQoL 5-dimensions 5-level; ERT, enzyme replacement therapy; ESA, elosulfase alfa; FEV1, forced expiratory volume in 1 minute; FVC, forced vital capacity; mths, months; MAA, market access agreement; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT population; PRO, patient-reported outcome; pts, patients; SD, standard deviation; uKS, urinary keratan sulphate; tx, treatment; yrs, years

As of [redacted], [redacted] patients were enrolled in the MAA (Table 25). [redacted] patients stopped treatment during the study period, although available assessment were included in the analysis: [redacted] voluntarily stopped for a variety of reasons ([redacted]. Another two patients were enrolled in the MAA and did not yet had follow-up data as they started within a year of the analysis and one patient had duplicated records. Of the [redacted] patients included in the analysis (Figure 11), [redacted] patients started elosulfase alfa in clinical trials prior to enrolling in the MAA, defined as Ex-Trial Patients ([redacted] in MOR-002, and [redacted] in MOR-004, MOR-007 or MOR-008); the remaining [redacted] patients started elosulfase alfa after enrolling in the MAA, defined as ERT-Naïve Patients.

Table 25. MAA patient demographics and baseline characteristics

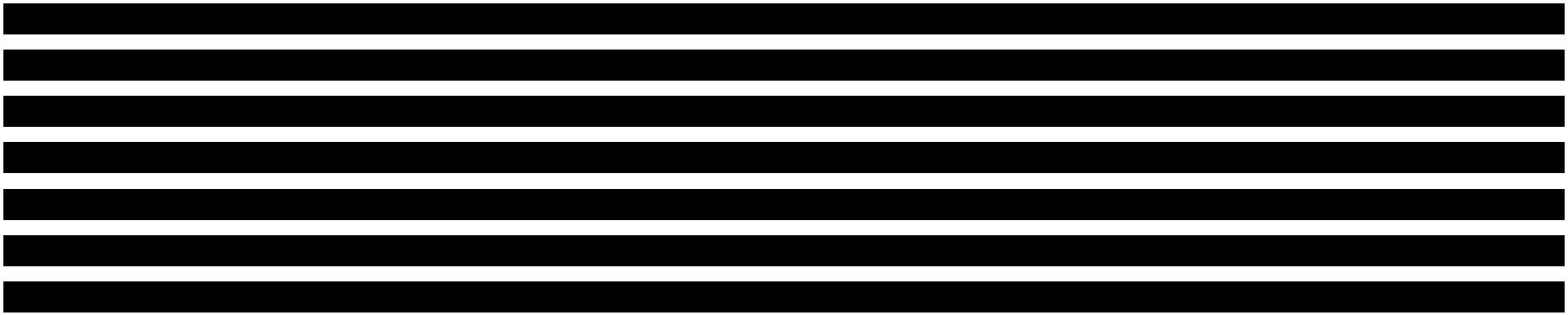
	Ex-Trial Patients (initiated treatment before MAA)	**ERT-Naïve Patients (initiated treatment in MAA)**
N	[redacted]	[redacted]
Female, number (%)	[redacted] ([redacted]	[redacted] ([redacted]%)
Age at enrolment, years		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
Treatment Duration, years		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]

Weight, kg		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
6MWT, meters		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
FVC, L		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
FEV1, L		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
Ejection fraction, %		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
uKS, µg/mg creatinine		
N	[redacted]	[redacted]

Mean (SD)	[redacted] ([redacted]	[redacted] ([redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]

N: number of patients

Figure 11. Flow chart of patient disposition in MAA analysis



Evaluation of clinical and patient-reported outcomes

The **clinical outcomes** collected as part of the MAA agreement include uKS, weight, 6MWT results without walking aids, pulmonary function (FVC and FEV1) and cardiac ejection fraction.

PRO measures include ADL, QoL, depression (for those over 13 years of age), and pain.

- **ADL** were monitored using the MPS HAQ. This questionnaire assesses self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting), mobility skills (dexterity, mobility, walking, stair climbing, and gross motor skills), and caregiver-assistance required in the performance of these activities (Hendriksz et al., 2018b). Total self-care and mobility domain scores range from 0 (not difficult at all) to 10 (extremely difficult) and 11 (unable to do). The total caregiver-assistance domain score ranges from 13 (independent) to 52 (complete assistance required) (Hendriksz et al., 2018b). Decreases in MPS-HAQ scores imply improvements.

- **QoL** was monitored using the EuroQol 5 dimensions, 5 levels (EQ-5D-5L) tool, a generic standardised measure of health status comprising five dimensions: Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression (EuroQol Group, 2019). EQ-5D-5L health states can be converted into a single summary index value (utility), ranging from “1” (representing perfect health) to “0” (representing death) using a UK tariff.

- **Pain** was measured using the Adolescent and Paediatric Pain Tool (APPT) in patients <18 years of age and the Brief Pain Inventory (BPI) in patients aged ≥18 years. The APPT is a validated tool to evaluate pain severity, location and description in children and adolescents aged 8 to 17 years (Jacob et al., 2014). The BPI Short Form (BPI-SF) is a widely used tool to rate

pain severity, pain location and the impact of pain on daily functioning (The Brief Pain Inventory: MD Anderson Cancer Society). Pain severity score in these tools, ranges from 0 (no pain) to 10 (worst possible pain/pain as bad as you can imagine).

- **Depression** was monitored using the Beck Depression Inventory, a 21-item self-report instrument, with higher total scores (ranging from 0 to 63) indicating more severe depressive symptoms (Beck et al., 1996).

PRO tools were completed on entry in the MAA and at least once before or at 12 months (see the complete assessment schedule in **Error! Reference source not found.** below). PRO tools were completed by either the patient or their parent/caregiver, d epending on the patient's age, either over the telephone or during a face-to-face interview with a patient organisation representative.

For each outcome, patients were measured against their pre-treatment baseline, if available. For those patients who did not have a pre-treatment baseline due to age, or when the variable was not measured at baseline for ex-trial patients, the first measure during the MAA period was used as baseline (see Patients should still undergo a baseline assessment prior to treatment initiation and regular follow-up assessments. However, the data collection as part of the NICE re-evaluation process of elosulfase alfa has now been completed. During the Extension Period (until December 2021), PROs will no longer be collected for the purposes of the MAA, and NHSE/NICE will rely on clinician reporting to assess compliance with maintenance criteria (via the Blueteq form).

Recommended assessments as per the MAA are summarised in **Error! Not a valid bookmark self-reference.** below and are aligned with the latest international guidelines (Akyol et al., 2019).

Table 7).

Statistical analyses

Baseline demographics and characteristics were summarised for all participants who completed ≥1 year of assessments. Descriptive statistics were summarised for absolute values over time and for the actual and percentage change for each measure from baseline. A two-sample t-test was used to compare the means of each population. A p-value <0.05 signifies that the means are statistically different.

Subgroup analyses were performed by trial history as a proxy for treatment duration (patients initiating treatment in the MAA since 2015, patients previously enrolled in MOR-002, and patients previously enrolled in other trials) and by age at treatment initiation (>18/≤18 years). Endurance (6MWT) and lung function (FVC and FEV1) data were compared with those of a cohort of untreated patients from the MOR-001 natural history study. Spearman correlation analyses between outcome data at baseline, 36 months of MAA, and change from baseline at 36 months in the MAA were conducted to investigate the relationship between outcomes.

The Morquio A Registry Study (MARS)

Study design

The Morquio A Registry Study (MARS) is a multicentre, multinational, observational registry for patients with MPS IVA).

MARS collects medical history, efficacy, and safety assessments in a voluntary manner via the recommended schedule of assessments for up to 10 years. MARS will enrol and collect data on patients over a period of at least 8 years from the date of first

marketing approval globally. Data on individual patients will continue to be collected for at least 2 years from the time that the last subject is enrolled or until MARS is completed.

MARS also collects additional data on patients who have completed the MOR-005 and MOR-007 clinical trials and who agree to participate in the registry. These patients will be enrolled into the appropriate sub-study for a minimum of 5 years from the time of the subject's enrolment in the respective clinical study. After the 5-year period, these patients may remain in MARS until the registry is complete.

Patients eligible to participate in this registry must have a laboratory-confirmed diagnosis of MPS IVA, be appropriately consented, and be willing to undergo assessments to establish baseline data or permit the Investigator to enter assessment data recorded prior to registry entry, if available in the patients' medical records.

MPS IVA patients are not required to receive elosulfase alfa to be eligible to participate in this registry. To participate in the registry sub-study for MOR-005 or MOR-007, patients must have completed either the MOR-005 or MOR-007 clinical trial and be appropriately consented into the sub-studies. Patients who become pregnant while participating in the sub-study who were receiving treatment with elosulfase alfa may also participate in a pregnancy sub-study. The only exclusion criterion for the registry and its sub-studies is current participation in any elosulfase alfa clinical trial. The number of registrants for the registry is not limited. Patients who discontinue prematurely will not be replaced.

Table 26. Summary of methodology of observational studies: US Expanded Access Program and MOR-AUS

Title	BMN 110 US Expanded Access Program	BMN 110 Phase 3B in Australian Patients (MOR-AUS)
Study name (acronym)	110-503	110-502 MOR-AUS
Author, Year	NCT01858103, 2014d	NCT01966029, 2019b
Design / population	USA EAP	Ph 3B in AUS pts
Intervention(s)	ESA 2.0 mg/kg qw	ESA 2.0 mg/kg qw
Comparator(s)	N/A	N/A
Population	Confirmed MPS IVA (GALNS activity in affected range, beta-galactosidase and a second lysosomal sulfatase activity within normal range) or molecular diagnostic test (two mutations in GALNS identified that have previously been associated with an enzyme defect)	≥12 months, confirmed MPS IVA (GALNS activity in affected range, beta-galactosidase and a second lysosomal sulfatase activity within normal range)
Objectives	To provide pts who have been diagnosed with MPS IVA access to ESA until commercial product is available. Collect additional information on safety and tolerability of ESA	To evaluate the safety and tolerability of ESA 2.0 mg/kg/wk in Australian pts with MPS IVA
Location/Study setting	USA, Puerto Rico	AUS
Study design	EAP	Multicenter OL, Ph 3B
Duration of study	NR	52 wks
Sample size	NR	13
Inclusion criteria	Diagnosed with MPS IVA as confirmed by either GALNS enzymatic test or molecular diagnostic test (two mutations in GALNS identified that have previously been associated with an enzyme defect).	Diagnosed with MPS IVA as confirmed by a documented GALNS enzymatic test. Age 12 months or older.
Exclusion criteria	Currently enrolled in an ongoing clinical study of ESA. Discontinued from a ESA clinical study secondary to a safety-related event. Use of any investigational product (other than ESA in a clinical study) or investigational medical device within 30 days prior to BL, or requirement for any investigational agent prior to completion of all	Previous tx with ESA. Known hypersensitivity to any of the components of ESA. Major surgery within 3 months prior to study entry or planned major surgery during the 48-wk tx period. Prior BMT or HSCT. Has used any investigational product, or investigational medical device, within 30 days prior to

Title	BMN 110 US Expanded Access Program	BMN 110 Phase 3B in Australian Patients (MOR-AUS)
	scheduled program assessments. Not a current US resident or expecting to have travel plans outside the US during the planned period of participation in the EAP that may interfere with dosing regimen, scheduled program visits and safety monitoring.	BL; or is required to use any investigational agent prior to completion of all scheduled study assessments. Concurrent disease or condition, including but not limited to, symptomatic cervical spine instability, clinically significant and/or progressive spinal cord compression, or severe cardiac disease that would interfere with study participation, or pose a safety risk, as determined by the Investigator.
Method of randomisation	N/A	N/A
Method of blinding	N/A	N/A
Treatment arms (NITT/ NmITT)	ESA 2mg/kg/wk	ESA (dosing NR)
Baseline differences	NR	NR
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	NR	52 wks (minimum)
Statistical tests	NR	NR
Primary outcomes (including scoring methods and timings of assessments)	NR	Safety analysis: AEs, SAEs, deaths, and AEs leading to study drug discontinuation, or study withdrawals, treatment-emergent AEs, infusion-associated AEs. Concomitant medications, clinical laboratory tests, vital signs, ECGs, immunogenicity results, analgesic medication use, results from routine physical examinations (including standard neurologic examinations), and cervical spine imaging will be summarised descriptively.
Secondary outcomes (including scoring methods and timings of assessments)	NR	Efficacy analysis: 6MWT, 3MSCT, uKS, urine creatinine. Anthropometric measurements, including standing height, length, sitting height, knee height (as clinically indicated), head circumference and weight. FEV1, FIVC, FVC, MVV. APPT, PedsQL, SF-36. Sleep Apnoea Test. Also a possibility for an EXT phase in which to assess these outcomes.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; AE, adverse event; APPT, adolescent pediatric and pain tool; AUS, Australia; BL, baseline; BMT, bone marrow transplant; EAP, expanded access program; ECG, electrocardiogram; ESA, elosulfase alfa; EXT, extension; FEV1, forced expiratory volume in 1 minute; FIVC,

forced inspiratory vital capacity; FVC, forced vital capacity; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; HSCT, haematopoietic stem cell transplantation; MVV, maximum ventilation volume; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT population; OL, open-label; PedsQL, paediatric quality-of-life; Ph, phase; qw, weekly; SAE, serious adverse event; SF-36, short form-36; uKS, urinary keratan sulphate; wks, weeks

Table 27. Summary of methodology of observational study: ESP MOR-EAP (Expanded Access Program in Spain)

Study name (acronym)	ESP MOR-EAP
Author, Year	Pintos-Morell et al., 2018
Design / population	ESP EAP, 7-17 yrs
Intervention(s)	ESA 2.0 mg/kg qw
Comparator(s)	N/A
Population	7-17 yrs, MPS IVA
Objectives	To report on the use of ESA tx in 7 pediatric pts from Spanish Morquio A Early Access Program (MOR-EAP)
Location/Study setting	ESP
Study design	EAP
Duration of study	8 mths
Sample size	7
Inclusion criteria	Confirmed diagnosis of MPS IVA (GALNS molecular genetic testing)
Exclusion criteria	Prior HSCT or concurrent disease or condition that would interfere with ERT
Method of randomisation	N/A
Method of blinding	N/A
Treatment arms (NITT/ NmITT)	N/A, data presented individually for each of the 7 pts
Baseline differences	BL data presented individually for each pt in Table 1 of FP
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	Pts were followed for 8 mths
Statistical tests	NR
Primary outcomes (including scoring methods and timings of assessments)	6MWT, 3MSCT, FVC, FEV1, FEV1/FVC ratio, Total urinary GAGs, Molecular analysis of GALNS mutations, EQ-VAS, Anthropometric measurements (weight, length, BMI), audiometry measurements, vital signs, electrocardiograms and echocardiograms, an

Study name (acronym)	ESP MOR-EAP
	ophthalmological examination, MRI of brain and spine, and radiographs of lower extremities and spine.
Secondary outcomes (including scoring methods and timings of assessments)	NR

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BL, baseline; BMI, body mass index; EQ-VAS, EuroQoL-5D visual analogue scale; EAP, expanded access program; ERT, enzyme replacement therapy; ESP, Spain; FEV1, forced expiratory volume in 1 minute; FP, full paper; FVC, forced vital capacity; GAGs, glycosaminoglycans; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; HSCT, haematopoietic stem cell transplantation; MOR-EAP, Spanish Morquio A Early Access Program; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT population; pts, patients; qw, weekly; yrs, years

Table 28. Summary of methodology of observational studies: MAPLE and BMRN58492

Study name (acronym)	MAPLE	BMRN58492
Author, Year	NCT02208661, 2018	NCT03204370, 2019a
Design / population	Psychological and QoL study before/after ESA in adult pts	Natural history study in atypical (less severe) pts 18-55 yrs
Intervention(s)	NR	ESA 1.0 mg/ml i.v. solution
Comparator(s)	N/A	N/A
Population	≥18 yrs, confirmed MPS IVA (clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing)	18-55 yrs, atypical (less severe) MPS IVA
Objectives	To assess psychological health with Morquio via a comparison of psychological issues and QoL before and after tx	To increase knowledge on the natural history of disease in adult pts with atypical MPS IVA, treated or not with ERT, and to develop new objective and robust clinical criteria to evaluate the efficiency of ERT over time, particularly in pts presenting a non-classical phenotype
Location/Study setting	USA	FRA
Study design	Observational	Prospective observational cohort
Duration of study	2 yrs	5 yrs
Sample size	12	9
Inclusion criteria	Documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and	MPS IVA pts, height > 1 m (non-classical phenotypes)

Study name (acronym)	MAPLE	BMRN58492
	documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA. At least 18 yrs old. Subject was a participant in MAP study (Ph I) and is now receiving (or plans to receive in the near future) ERT in the EAP or commercial setting. If receiving ERT for the tx of MPS IVA, subject has been on tx for < 1 yr. -or- Subject was not enrolled in MAP study, but plans to start receiving ERT for MPS IVA in near future and is willing to take all BL questionnaires which were included in MAP, prior to beginning ERT.	Tx by ERT or not, followed in expert centre, affiliated to a health insurance system
Exclusion criteria	Previous tx with ERT prior to participation in ph 1 (MAP). Previous HSCT Clinically significant disease (except MPS IVA), including clinically significant cardiovascular, hepatic, immunologic, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstances that, in the opinion of the investigator, would confound the effects of MPS IVA upon study variables.	Pts affected by another disease
Method of randomisation	N/A	N/A
Method of blinding	N/A	N/A
Treatment arms (NITT/ NmITT)	NR	ESA 1mg/ml i.v.
Baseline differences	NR	NR
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	Self-reported questionnaire every 6 mths for 2 yrs	Pts will be followed up for 5 yrs
Statistical tests	NR	NR

Study name (acronym)	MAPLE	BMRN58492
Primary outcomes (including scoring methods and timings of assessments)	ASEBA	6MWT
Secondary outcomes (including scoring methods and timings of assessments)	BPI, SF-36	NR

Abbreviations: 6MWT, 6-minute walk test; ASEBA, Aschenbach System of Empirally Based Assessment; BPI, Brief Pain Inventory; EAP, expanded access program; ERT, enzyme replacement therapy; ESA, elosulfase alfa; FRA, France; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; HSCT, haematopoietic stem cell transplantations; i.v., intravenous; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT population; Ph, phase; pts, patients; SF-36, short form-36; tx, treatment; USA, United States of America; yrs, years

Table 29. Summary of methodology of observational studies: DEU PRO study, IQ study, Manchester Home Infusion study, Long-term Safety Analysis PRO survey in caregivers, and Hearing study

Study name (acronym)	**PRO study**	**IQ study**	**Manchester UK home infusion study**	**Long-term safety analysis (>48 wks exposure)**	**PRO survey in caregivers**	**Hearing study**
Author, Year	Lampe et al., 2015	Rigoldi et al., 2014	Finnigan et al., 2018	Harmatz et al., 2013a	Hendriksz, Lavery et al., 2014d	Nagao et al., 2018
Design / population	PRO study, 14 adults aged 18-54 yrs and 10 children aged 10-17 yrs	IQ study	Home infusion study, Manchester UK, pts 4-16 yrs	Long-term safety analysis (>48 wks exposure)	PRO survey in caregivers to MPS IVA pts	Hearing study, 13 MPS IVA and 1 MPS IVB; aged 12-38 yrs
Intervention(s)	NR	NR	ESA 2.0 mg/kg qw	ESA 2.0 mg/kg qw	N/A	NR
Comparator(s)	N/A	N/A	N/A	N/A	N/A	N/A
Population	14 adults aged 18-54 yrs and 10 children aged 10-17 yrs, MPS IVA	MPS IVA	4-16 yrs, MPS IVA	MPS IVA	≥18 yrs, 1ry caregiver of at least 1 MPS IVA pt	13 MPS IVA and 1 MPS IVB; aged 12-38 yrs
Objectives	To determine correlation between PRO and clinical outcomes in a German cohort. Authors also examined whether these relationships were consistent in	To investigate cognitive involvement in MPS IVA	Authors reviewed their experience with home ERT tx in children with MPS IVA and demonstrated criteria required to ensure successful home tx programme	To assess safety of ESA 2mg/kg/wk with MPS IVA	To evaluate global burden among primary caregivers of pts with MPS IVA. Collected outcomes included self-reported time spent on caregiving, proportion of daily	To examine hearing function in pts with MPS IV (mainly MPS IVA) and to correlate auditory phenotype with skeletal severity (measured as short stature) and/or ADL

Study name (acronym)	PRO study	IQ study	Manchester UK home infusion study	Long-term safety analysis (>48 wks exposure)	PRO survey in caregivers	Hearing study
	children (<18 yrs) and in adult (>=18 years) patients with MPS IVA				activities requiring caregiver assistance, and how pt's age and wheelchair use affect these. In addition, the impact of caregiving on the caregivers' relationship with family and friends, physical and mental health, and employment status and income was evaluated	
Location/Study setting	DEU	NR, author ITA	UK	NR, author USA	INT, 5 countries (BRA, COL, DEU, ESP, TUR)	USA
Study design	Voluntary, single-assessment, cross-sectional, paper-based survey	Prospective cohort study	Report	Safety analysis	Voluntary, single-assessment, cross-sectional, paper-based survey	Prospective cohort study
Duration of study	6 mths	NR	NR	1-12 wk and >48 wk tx intervals were used to assess AE frequency	Jun 2012-Apr 2013	NR
Sample size	24	13	23	52	56	14 (13 MPS IVA, 1 MPS IVB)
Inclusion criteria	Confirmed diagnosis of MPS IVA, (genetic testing or reduced GALNS activity) 7 yrs of age (some exceptions were made due to limited no. of pts) and able to speak, write, and understand their language.	NR	NR	>48 wks of ESA 2mg/kg/week exposure	Caregivers were recruited following enrolment of their family member who had MPS IVA in PRO survey. Caregiver burden evaluated in adult (>=18 yrs old) carers who served as primary caregiver of at least 1	Diagnosed biochemically with MPS IV

Study name (acronym)	PRO study	IQ study	Manchester UK home infusion study	Long-term safety analysis (>48 wks exposure)	PRO survey in caregivers	Hearing study
					pt with MPS IVA in 5 countries with strong patient advocacy/support groups and relatively fair no. of pts. Eligible caregivers had to be able to speak, write, and understand both the verbal and written language of their country	
Exclusion criteria	NR	NR	NR	NR	NR	NR
Method of randomisation	N/A	N/A	N/A	N/A	N/A	N/A
Method of blinding	N/A	N/A	N/A	N/A	N/A	N/A
Treatment arms (NITT/ NmITT)	Data reported separately for adults (n=14) and children (n=10)	NR	ESA 2mg/kg/week	ESA 2mg/kg/wk	NR	N/A, data presented individually for each of the 14 pts
Baseline differences	Male (%)- Adults - 78.6, Children 50	13 MPS IVA pts with WAIS- R 2pts (37yrs, 28yrs); WISC III 9pts (6-16yrs); WPPSI III 1 pt (5yrs); Griffiths 1 pt (3.5yrs)	NR	To account for varying durations of follow-up in ongoing studies, frequencies of AEs were reported standardised on an annualised basis	Most caregivers (82.1%) were mothers of pts with MPS IVA	8 of the pts with MPS IVA had received ERT for 1 to 5 yrs
How was follow-up conducted? Duration of follow-up,	PRO-survey conducted across a 6-month time window. Clinical outcomes data obtained from Mainz Clinical database and	NR	NR	Unclear, 1-12 wk and >48 wk tx intervals were used to assess AE frequency	Jun 2012-Apr 2013	All the audiological data were obtained in a sound proof booth. Participant's demographic information,

Study name (acronym)	PRO study	IQ study	Manchester UK home infusion study	Long-term safety analysis (>48 wks exposure)	PRO survey in caregivers	Hearing study
participants lost to follow-up	MorCAP natural history study database to coincide with this window.					medical/health history including frequency of ear infection, and functional ADL were obtained with a questionnaire
Statistical tests	Variance regression analyses providing Pearson's coefficients (R), slopes as well as coefficients of determination (adjusted R^2)	NR	NR	NR	Due to the limited number of pts in some of the mobility subgroups, most results are presented as descriptive statistics. A t-test was used to evaluate the statistical significance of differences in mean age between mobility/wheelchair groups for the entire pt group (both children and adults)	Pearson's correlation coefficients, correction analysis
Primary outcomes (including scoring methods and timings of assessments)	6MWT, 3MSCT, and joint range of motion as measures for endurance/mobility, FVC and MVV, and height. EQ5D-5L and patients' rating of their ability to walk, climb, or breathe		Criteria for safe transfer to home therapy were set out	Subject-year frequency of AEs, IARs, discontinuation due to AE requiring medical intervention	Caregiver questionnaire (demographics (eg, age and gender), family relationships, and social characteristics (education, employment status, impact of MPS IVA on relationships and finances and support received from family/friends, society, and health care	Distortion products otoacoustic emissions, abnormal auditory brainstem responses, pure tone average score, ADL score, BMI, prior ERT use

Study name (acronym)	PRO study	IQ study	Manchester UK home infusion study	Long-term safety analysis (>48 wks exposure)	PRO survey in caregivers	Hearing study
					professionals) Level of assistance caregiver needed to provide for a pt to perform daily activities evaluated according to pts' mobility level MPS HAQ. Caregiving hours according to wheelchair use/mobility level. Zarit Burden Interview global score according to wheelchair use/mobility level. Caregivers of adult pts and children were asked to indicate whether, as a result of caring for pts with MPS IVA, they had clinical (stress, lack of sleep, ulcers, gastrointestinal issues, back pain from carrying) or mental (feeling burdened, anxiety, depression) health issues and whether they received therapy or medicines for their emotional and psychological health	
Secondary outcomes	NR	NR	NR	NR	NR	NR

Study name (acronym)	PRO study	IQ study	Manchester UK home infusion study	Long-term safety analysis (>48 wks exposure)	PRO survey in caregivers	Hearing study
(including scoring methods and timings of assessments)						

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; DEU, Germany; EQ-5D-5L, EuroQoL 5-dimensions 5-level; FVC, forced vital capacity; IQ, intelligence quotient; MPS, mucopolysaccharidosis; MVV, maximum ventilation volume; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT population; PRO, patient-reported outcome; pts, patients; yrs, years; AE, adverse event; ERT, enzyme replacement therapy; ESA, elosulfase alfa; IAR, infusion associated reactions; MPS, mucopolysaccharidosis; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT population; tx, treatment; UK, United Kingdom; USA, United States of America; wk, week; ADL, activities of daily living; BMI, body mass index; BRA, Brazil; COL, Columbia; DEU, Germany; ERT, enzyme replacement therapy; ESP, Spain; HAQ, health assessment questionnaire; INT, International; MPS, mucopolysaccharidosis; NITT, number of patients in ITT population; NmITT, number of patients in modified ITT population; PRO, patient-reported outcome; pt, patient; TUR, Turkey; yrs, years.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Table 30 below summarises citations that are linked providing methods and/or results data for the included studies. Patients in the Phase 1/2 MOR-002 study could continue into MOR-100. Patients in the Phase 3 RCT MOR-004 could continue in an open-label extension (OLE) MOR-005 study.

Table 30. Summary of linked citations

Trial ID	Main publication author, year	Intervention	Comparator(s)	Associated references	Linked publication content
MOR-002	Hendriksz, Santra et al., 2018a	ESA (Dose-escalation across 36 wks, divided into 3 consecutive 12-wk intervals, at doses of 0.1, 1.0, and 2.0 mg/kg qw)	N/A	Hendriksz, Vellodi et al., 2013c	Reports 156 wk data
				Registry record (NCT 2014a)	Used for inclusion/exclusion criteria Results reported on registry record
				Registry record Euctr GB, 2009)	Results reported on registry record
MOR-100	Hendriksz, Santra et al. 2018a	ESA (2.0 mg/kg qw ESA 192 wks)	N/A	Registry record (NCT, 2015)	Used for inclusion/exclusion criteria Results reported on registry record
				Registry record (Euctr GB, 2010)	Results reported on registry record
MOR-004	Hendriksz, Burton et al., 2014b	ESA 2.0 mg/kg qw ESA 2.0 mg/kg qow	PLA	Melton et al, 2017	Neutralising antibody titer shown to not be correlated with clinical outcomes
				Hendriksz, Guigliani et al., 2015d	Composite endpoint, MPS HAQ, tertiary endpoints
				Registry record (NCT 2014b)	Results reported on registry record
				Registry record (Euctr IT, 2011a)	Results reported on registry record
MOR-005	Hendriksz, Parini et al., 2016c	ESA 2.0 mg/kg qw ESA 2.0 mg/kg qow	N/A, OLE	Hughes et al., 2017	Adult sub-population results to wk 120
				Hendriksz, Parini et al, 2018b	MPS HAQ
				Hendriksz, Berger et al., 2016b	Reports respiratory function outcomes
				Registry record (NCT, 2014c)	Results reported on registry record
				Registry record (Euctr IT, 2011b)	Results reported on registry record

Trial ID	Main publication author, year	Intervention	Comparator(s)	Associated references	Linked publication content
MOR-006	Harmatz et al., 2017	ESA 2.0 mg/kg qw	N/A	Registry record NCT, 2016)	Results reported on registry record
MOR-007	Jones et al., 2015	ESA 2.0 mg/kg qw	N/A	Registry record (NCT, 2017)	Results reported on registry record

Abbreviations: ESA, elosulfase alfa; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire; OLE, open label extension; PLA, placebo; qow, every other week; qw, weekly; wk, week

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

As summarised in Tables 15-30 above, each of the studies is different in terms of: inclusion and exclusion criteria, primary endpoints, secondary and other outcomes measures, study groups and study design.

MOR-004 included patients above the age of 5 years and with an ability to walk between 30m to 325m in 6 minutes, in order to ensure maximum sensitivity to the primary end-point, The study was limited to a duration of 24 weeks and excluded participants who had had major surgery within 3 months prior to study entry or planned major surgery during the 24-week treatment period.

Alternatives studies have been designed to evaluate the efficacy and safety of elosulfase alfa in those additional sub-populations. MOR-007 was conducted exclusively in a population of MPS IVA patients <5 years of age, who were not eligible to participate in the pivotal Phase 3 study. MOR-006 includes patients with limited mobility, whereas MOR-008 includes only patients aged at least 7 years who can walk at least 200 metres in the 6MWT.

Moreover, as noted in section 6 above, the clinical manifestations of MPS IVA are extremely heterogeneous, due in part to the large number (more than 220) of genetic mutations that have been identified so far. For example, the study participants in the Phase 3 MOR-004 study had a wide variation in their functional impairment and organ system involvement at baseline.

The demographic details and baseline characteristics of the participants in MOR-004, MOR-005, MOR-007, MOR-002 and MOR-100 are given in section **Error! Reference source not found.**.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify

the rationale and state whether these analyses were pre-planned or post-hoc.

Pre-specified subgroup analyses were undertaken on the primary analysis of the primary endpoint in MOR-004.

In MOR-004, the Week 24 change from Baseline in the 6MWT distance was the primary efficacy endpoint.

The primary analysis of the primary endpoint was the analysis of covariance (ANCOVA) of the Week 24 change from Baseline in the 6MWT measurement using a model with treatment, age stratification (5–11, 12–18, ≥ 19 years), and Baseline 6MWT stratification (≤ 200 metres and > 200 metres) as factors. Each active treatment group was compared to the placebo group using contrasts and P values calculated using the t test. Least squares (LS) means and confidence interval (CI) for the two treatment effects were also provided. There were only 2 missing assessments of 6MWT, and the two values were imputed using multiple imputation.

A number of additional analyses were undertaken to investigate the robustness of the primary analysis results on the primary endpoint, and to explore the uniformity of the overall treatment effect. To explore uniformity of treatment effect in MOR-004, pre-specified analyses were performed to determine the possible interaction of subgroups with treatment using the ANCOVA model of the primary analysis with an additional interaction-by-subgroup covariate term.

In MOR-004, 6MWT results were assessed in sub-populations based on screening 6MWT categories (≤200 metres and > 200 metres), age group at baseline (5-11, 12-18, ≥19 years), sex (female vs. male), race (white vs. non-white), and region (North America, Europe, other).

Overall, the subgroup analyses 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/week

dose regimen. P values for the test for interaction ranged from 0.1224 to 0.8921 for elosulfase alfa 2.0 mg/kg/week versus placebo.

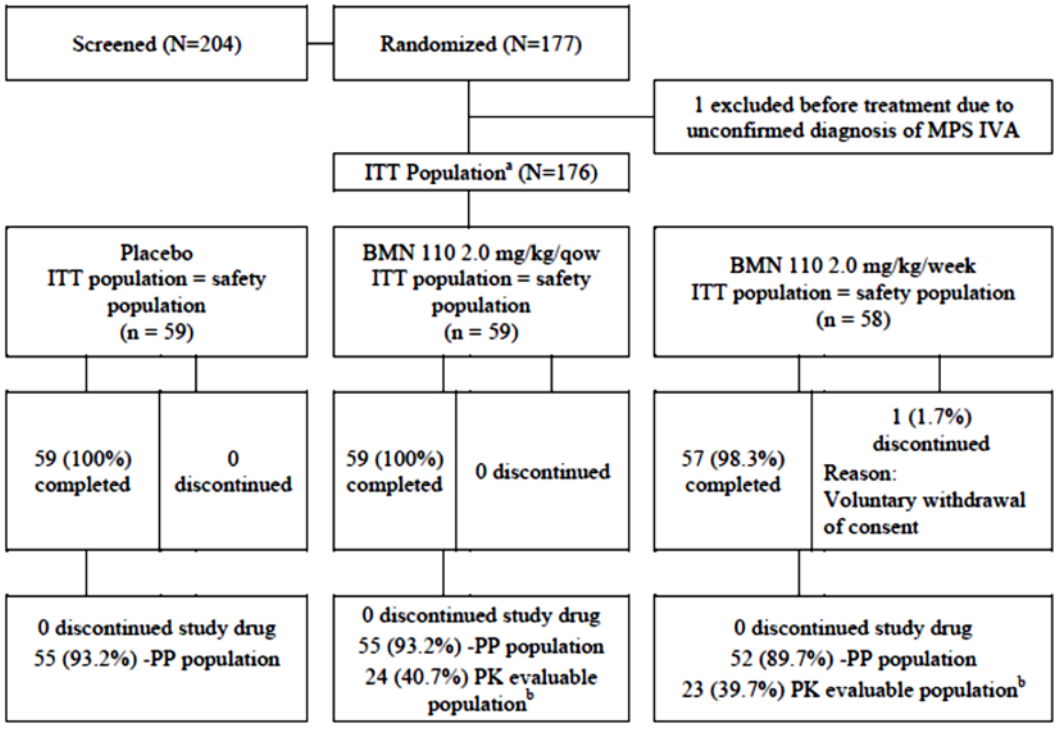
As discussed further in the clinical results section 9.6, the long-term evidence from the clinical programme and from real-world studies confirms that a wide variety of MPS IVA patients can benefit from treatment with elosulfase alfa. As discussed in the previous NICE Evaluation Committee sessions, there are no *a priori* criteria to define which patient or patients will benefit most from the treatment.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

CONSORT flow charts are presented here for the participants in the three RCTs: MOR-004, MOR-005, MOR-008.

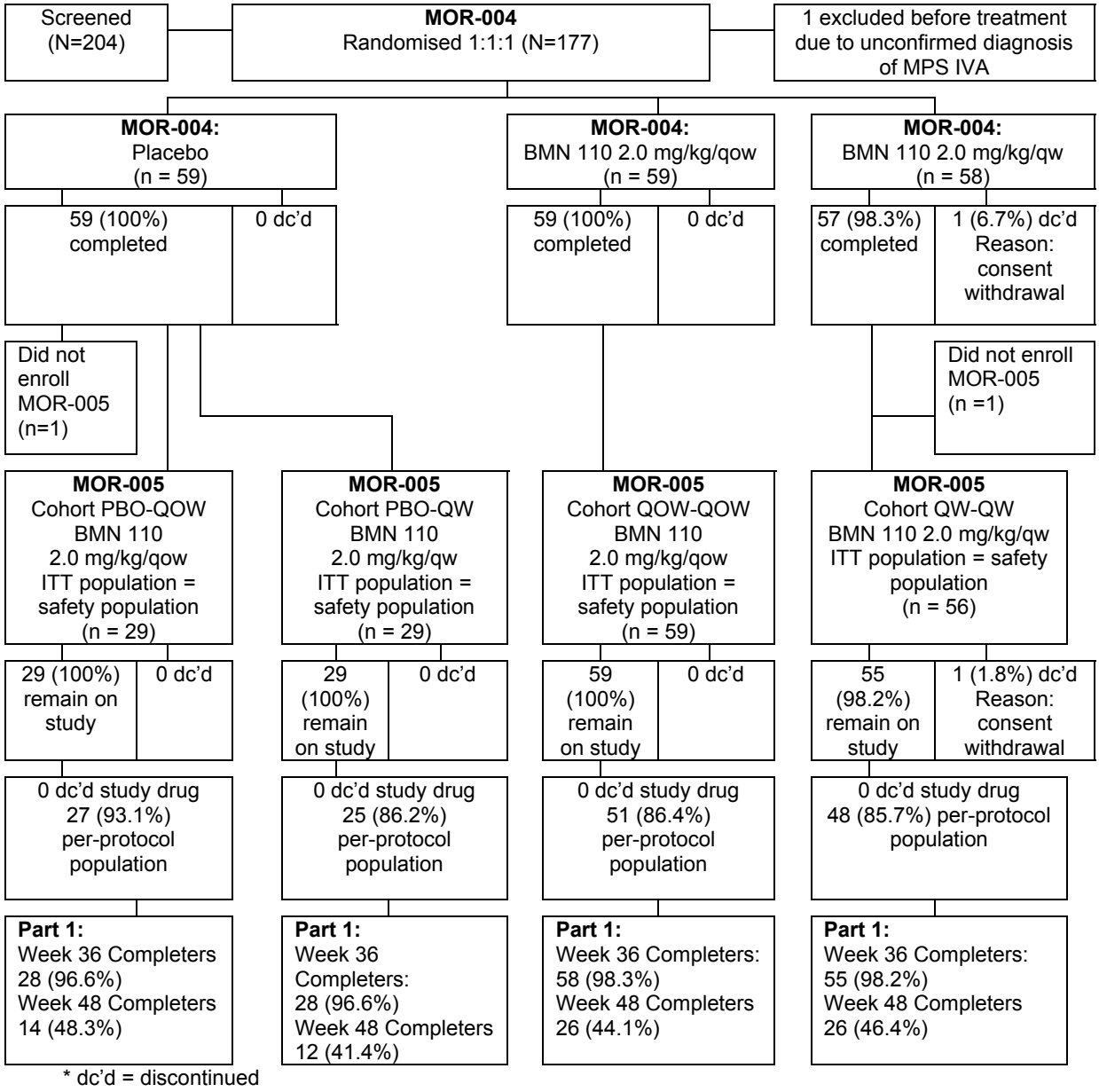
The disposition of participants in the MOR-004 study is shown in Figure 12.

Figure 12. Disposition of participants in MOR-004



The disposition of participants in the MOR-005 study is shown in Figure 13.

Figure 13. Disposition of participants in MOR-005



* dc'd = discontinued

The disposition of participants in the MOR-008 study is shown in Table 31.

Table 31. Disposition of participants in MOR-008

Category	BMN 110 2.0mg/kg/week	BMN 110 4.0mg/g/week
Subjects randomised	15	10
Subjects treated (safety)[a]	15 (100%)	10 (100%)
Subjects who completed the study	15	10
Subjects who discontinued from the study	0	0

[a] The safety population consists of all subjects who receive any study drug and it is analysed according to the actual treatment received.

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

In MOR-004, only 1 patient from the ITT population (n=176) failed to complete the study. The patient voluntarily withdrew consent to participate prior to administration of the first study treatment. Of the 175 patients who completed MOR-004, 173 of them were enrolled into the open label extension study, MOR-005. One subject in the 2.0 mg/kg/qw group and one subject in the placebo group of MOR-004 did not sign an informed consent for MOR-005 and so did not enter the extension study.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

Risk of bias assessment in RCTs is reported in Table 32 and in observational studies in Table 33. As the observational studies were single-arm studies, the Institute of Health Economics (IHE) QA checklist for case-series was utilised (Guo et al., 2016).

Table 32. Critical appraisal of randomised controlled trials (Table C7)

Study name	**MOR-004 / Hendriksz et al. 2014b**	
Question	**Response (Y/N/Unclear/N/A)**	How is the question addressed in the study?
Was randomisation carried out appropriately?	Unclear	The exact method of generating the randomisation sequence was NR. However, randomisation was stratified by screening 6MWT category (<=200 and >200 m) and age group (5–11, 12–18, >=19 yrs old), suggesting a centralised procedure.
Was the concealment of treatment allocation adequate?	Unclear	Concealment not specified
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Tx arms balanced at BL
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Described as double-blind. Statement "Patients, investigators and site personnel were blinded to treatment assignment throughout the study and until the final analysis was complete". Also, patients randomised to the arm with (active) treatment every other week were given placebo infusions on alternative weeks to mask active drug weeks.
Were there any unexpected imbalances in dropouts between groups?	No	Discontinuations were 1/58 (1.7%) in ESA 2.0 mg/kg/wk arm and 0/59 (0%) in ESA 2.0 mg/kg qow and PLA arms. The 1 pt withdrew consent after the first infusion due to logistical difficulties attending study visits, not because of safety concerns
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No indication of selective reporting
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT analysis performed. MPP results also presented. Methods to account for missing data were described: in the primary outcome, the 2 missing 6MWT values were imputed using

Study name	**MOR-004 / Hendriksz et al. 2014b**	
Question	**Response (Y/N/Unclear/N/A)**	How is the question addressed in the study?
		multiple imputation. Over 99% of subjects completed study.
Additional info	N/A	It is possible that there is some risk of bias at study level, because although the blinding was clearly reported, the randomisation sequence and allocation concealment was NR. Sample size was based on an expected benefit over PLA of 40m on 6MWT. The actual benefit was 22.5m (smaller effect), suggesting that more robust measures may have been obtained if a larger sample size had been planned. Authors indicate that 3MSCT may be less suitable for Morquio patients than for MPSVI patients, as Morquio patients have more severe skeletal dysplasia and joint abnormalities, and that 24 weeks might not be sufficient time for a difference to be observable between ESA and placebo. Also, 3MSCT was a secondary outcome, and the sample size was based on 6MWT. There is a possibility therefore that the active arms showed no statistically significant difference vs. PLA in 3MSCT change from BL because of being underpowered. It could also be that this test is less appropriate in Morquio A.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BL, baseline; ESA, elosulfase alfa; ITT, intention-to-treat; m, metre; MPP, modified per protocol; N/A, non-applicable; NR, not reported; PLA, placebo; pt, patient; wk, week; yrs, years

Table 32 continued (Table C7 continued)

Study name	**MOR-005 / Hendriksz et al. 2016c**	
Question	**Response (Y/N/Unclear/N/A)**	How is the question addressed in the study?
Was randomisation carried out appropriately?	Unclear	The exact method of generating the randomisation sequence was NR. Only those pts who had been on PLA in MOR-004 were re-randomised without stratification (1:1 ratio) to either ESA 2.0mg/kg/wk or qow. Pts randomised in MOR-004 to an ESA tx arm remained on that tx arm in MOR-005 part 1. At a specific date (01-Dec-2012), in MOR-005 part 2 (the OLE), all pts were switched to ESA 2.0mg/kg/wk, the recommended dose after review of final results from MOR-004 and the DMC.
Was the concealment of treatment allocation adequate?	Unclear	Concealment not specified
Were the groups similar at the outset of the study in terms of prognostic factors?	No	Randomisation on entry to MOR-005 was not stratified (as MOR-005 objective was to evaluate long-term efficacy and safety of active tx, and to enable pts previously randomised to PLA to receive ESA until MAu allowed access to commercial product) and a chance imbalance occurred in MOR-005 BL characteristics (age and endurance measures) resulting in better 6MWT and 3MSCT results for (previously on PLA) pts now on ESA 2.0mg/kg qow than for (previously on PLA) pts now on ESA 2.0mg/kg/wk.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Described as double-blind. Further, masking described as quadruple: participant, care provider, investigator, outcomes assessor
Were there any unexpected imbalances in drop-outs between groups?	No	Discontinuations were 1/56 (1.8%) from Part 1 and 1/56 (1.8%) from Part 2 in ESA 2.0 mg/kg/wk arm (weekly dose in both MOR-004

Study name	**MOR-005 / Hendriksz et al. 2016c**	
Question	**Response (Y/N/Unclear/N/A)**	How is the question addressed in the study?
		and MOR-005) and 0/59 (0%), 0/29 (0%) and 0/29 (0%) in ESA 2.0 mg/kg qow (qow dose in both MOR-004 and MOR-005) and PLA-QOW and PLA-QW cohorts.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No indication of selective reporting
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT analysis performed. MPP results also presented. MPP population excluded pts who had orthopaedic surgery and those not complying with protocol recurrently. Missed infusions were used to indicate compliance; pts missing ≥20% of their scheduled ESA infusions during MOR-005 were classified as non-compliant (14 pts) and excluded from MPP population. Total excluded from MPP population 49 pts.
Additional info	N/A	Authors comment that variable timing of transition to weekly dosing (from week 36 to week 96) precludes comparison of dosing regimens. Comparison further made difficult by small sample sizes in cohorts of pts originally randomised to PLA. Hence MPP population compared to MorCAP data.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BL, baseline; DB, double-blind; DMC, data monitoring committee; ESA, elosulfase alfa; ITT, intention-to-treat; MAu, marketing authorisation; MPP, modified per protocol; N/A, non-applicable; NR, not reported; OLE, open label extension; PLA, placebo; pts, patients; qow, every other week; qw, weekly; tx, treatment; wk, week

Table 33. Critical appraisal of single-arm studies

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
Was the hypothesis/aim/objective of the study clearly stated?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	The objectives were to identify the optimal efficacious dose of ESA and assess safety and tolerability in a ph 1/2 dose finding trial in MPS IVA pts aged 5-18 yrs.	The objective was to assess the efficacy and safety of ESA in more severely disabled MPS IVA pts (limited ambulation unable to walk 30m or more in 6MWT).	The primary objective was to assess the safety and tolerability of ESA 2.0 mg/kg/wk in MPS IVA pts <5 yrs of age. The 2ry objectives were to assess its ability to reduce uKS and to impact growth velocity.
Was the study conducted prospectively?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	Study conducted over 48 wks, with pts continuing afterwards into a long-term EXT (MOR-100)	Study conducted over 48 wks, with pts continuing afterwards into a EXT providing safety data to 96 wks.	Study conducted over 52 wks.
Were outcome assessors blinded to the intervention that patients received?	Yes, partial/unclear, no	No	No	No
	Justification	Study was an open-label, single arm study, with all patients receiving the same tx schedule (dose-escalation in first 36 wks and continuation period (36-48wks). Outcomes were NR to have been measured at	Study was an open-label, single arm study, with all patients receiving the same tx dose. Outcomes were NR to have been measured at central laboratory.	Study was an open-label, single arm study, with all patients receiving the same tx dose. Outcomes were NR to have been measured at central laboratory.

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
		central laboratory and also NR if outcome assessors knew the trial design/tx escalation schedule or not		

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes, partial/unclear, no	Yes	Unclear	Yes
	Justification	Yes, probably. 6MWT (ATS guidelines) and 3MSCT appear to be objective measures and standard pulmonary function tests employed (FVC, FEV1, MVV), but limited detail provided as to methods used.	The method for T25FW testing was referenced (Polman and Rudick 2010) and differences compared to this stated. Customisation of FDT test method was shown in a video (suppl. File 4). However, the authors also indicate that there were considerable challenges in objectively measuring the impact of ESA in this severely disabled MPS IVA population (e.g. sometimes tests were not performed if the child was in pain).	The methods for uKS normalised to creatinine and for growth outcomes were detailed and further described in Suppl. Appendix S3 and S4, respectively.
Were the relevant outcome measures made before and after the intervention?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	6MWT, 3MSCT and pulmonary function measured at BL and then at regular intervals.	Results were reported at BL and at various timepoints	Results were reported at BL and at various timepoints to wk 52 in FP

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
Were the statistical tests used to assess the relevant outcomes appropriate?	Yes, partial/unclear, no	Yes	Unclear	Yes
	Justification	Descriptive statistics were used in MOR-002. In MOR-100 (the EXT), because pts entered MOR-100 with different durations of prior tx exposure, a mixed-model analysis, including repeated measures for pts and months was employed to estimate LS outcomes by tx duration.	The safety analyses were appropriately (mITT population analysed defined - as is standard -as all pts randomised and received at least one dose of study drug). The efficacy analyses were not analysed on an ITT basis but on a MPP population. Authors indicate the reason for this was that several pts from ITT population were non-compliant with protocol or did not stay in the study for the 48 wk period due to logistical issues, acute disease issues or ADRs to study drug. Criteria for the MPP population were also changed, so that pts missing 20% or more of infusions were excluded from the analysis set.	Descriptive statistics were used in MOR-007. Efficacy population was all pts who had received at least one dose of study drug and had at least one post-baseline efficacy measurement. Safety population was all pts who had received at least one dose of study drug.

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
Was follow-up long enough for important events and outcomes to occur?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	Results were reported in MOR-002 up to 48 wks and in MOR-100 for 192 wks	Results were reported in MOR-006 up to 48 wks and in its EXT on the registry record up to 96 wks	Results were reported in MOR-007 for the primary tx phase up to 52 wks in FP and registry record. There is an EXT phase also of up to 156 wks plu 1 extra wk for final assessments.
Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	SD of 6MWT, 3MSCT and of FVC, FEV1 and MVV were all reported.	SE for respiratory function outcomes reported and for the T25FW	SD for % change from BL in uKS reported.
Were the conclusions of the study supported by the results?	Yes, partial/unclear, no	Yes	Yes	Yes

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
	Justification	The study concluded that from the clinical measures the pts did not appear to have progressive deterioration in endurance, pulmonary function or functional capabilities, but added that attributing this to ESA tx specifically could not be done in the absence of a PLA group.	The study concluded that ESA had an acceptable safety profile even in severely disabled MPS IVA pts who may not tolerate mild infusion related reactions, and suggests benefit potential in these pts.	The study concluded that the results suggest a favourable benefit/risk profile for ESA in paediatric MPS IVA pts < 5 yrs of age.
Were the characteristics of the patients included in the study described?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	Several BL characteristics were described (Table 1), including age, sex and BL endurance parameters (6MWT, 3MSCT). Ethnicity and region are further given in the registry record.	Wide range ofl BL characteristics were described, per individual in the MPP population and mean [SE] data reported (Table 1), including age, sex, age at diagnosis, length, weight, FDT, T25FW speed and method of ambulation in T25FW. Ethnicity and region of enrolment further reported in registry record.	Wide range ofl BL characteristics were described in FP (Table 1), including age, sex, race, ethnicity, normalised uKS, length and standing height. Region of enrolment further reported in registry record (ITA, UK, USA).

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	Clearly stated on the registry record (though not in the FP)	Clearly stated on the registry record (though not in the FP)	Clearly stated in FP and on the registry record.
Did patients enter the study at a similar point in the disease?	Yes, partial/unclear, no	Unclear	Unclear	Unclear
	Justification	Unclear as no details reported on age at diagnosis. The paper indicated there was a wide range of functional impairment due to the heterogeneity of disease, and pts ranged in age from 4-16 yrs, so it is plausible that pts entered the study at different points in the disease.	Possibly. A major inclusion criterion is the inability to walk 30m in the 6MWT at the screening visit, so pts all entered the study having reached a limited ambulation stage. However, clinical heterogeneity was indicated by the authors and although the age at diagnosis was for most pts between 1-5 yrs, one patient was diagnosed aged 42.4 yrs.	Unclear as no details reported on age at diagnosis. However, since all pts were <5 yrs at enrolment, it is possible that pts entered the study at a broadly similar stage in the disease.
Was the intervention of interest clearly described?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	ESA 0.1 (wks 1-12), 1.0 (wks 13-24) and 2.0 (wks 25-36) and 1.0 (wks 36-48) mg/kg/wk given i.v. over 4-5 hrs.	ESA 2.0 mg/kg/wk throughout given i.v. over 4-5 hrs.	ESA 2.0 mg/kg/wk throughout given i.v. over approximately 4 hrs. More detailed infusion procedure given in Suppl. Appendix S2.

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
Were additional interventions (cointerventions) clearly described?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	Prior to infusion antihistamines were given as prophylaxis for potential hypersensitivity reactions.	Approximately 30 min to 1 hr prior to infusion non-sedating antihistamines were given to all pts as prophylaxis for potential hypersensitivity reactions. For pts with a history of reactions temporally related to drug infusion or other risk factors, a sedating antihistamine could be considered, and premedication with additional agents such as H2 blockers, montelukast sodium, or steroid.	All pts received antihistamines within 1 hr prior to infusion. Choice of antihistamine was at the discretion of the investigator. However, non-sedating antihistamines were suggested for use first.
Were losses to follow-up reported?	Yes, partial/unclear, no	Yes	Yes	Unclear
	Justification	2 pts / 20 (10%) withdrew from the 0.1 mg/kg/wk dose escalation period, one due to a type I hypersensitivity reaction, and the second (the sibling of the other withdrawal) due to pt request (in abscence of AEs).	3 pts / 15 (20%) withdrew, 2 due to grade 3 tx-related AEs (infusion related reaction and hypersensitivity) and 1 due to recurrent UTIs unrelated to tx.	Although the FP is clear that no pt discontinued due to an AE and that all pts were included in efficacy analyses, the overall numbers discontinuing per se were NR in the FP or on the registry record.

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
Were the adverse events reported?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	AEs, ADRs, SAEs and tx-related SAEs were reported and that there were no deaths.	AEs, ADRs, SAEs and tx-related SAEs were reported and that there were no deaths. The SAE data are on the registry record, not in the FP.	AEs, ADRs, SAEs and tx-related SAEs were reported and that there were no deaths.
Were the cases collected in more than one centre?	Yes, partial/unclear, no	Yes	Yes	Yes
	Justification	Birmingham, London and Manchester, in England	Multiple centres in USA, Germany and UK	2 centres in USA, 1 in ITA, 1 in TWN and 1 in UK
Were patients recruited consecutively?	Yes, partial/unclear, no	Unclear	Unclear	Unclear
	Justification	NR if this was the case, aside from the eligibility criteria being applied	NR if this was the case, aside from the eligibility criteria being applied	NR if this was the case, aside from the eligibility criteria being applied
Were both competing interests and sources of support for the study reported?	Yes, partial/unclear, no	Yes	Yes	Yes

	Trial ID	MOR-002/MOR-100 Hendriksz, Santra et al., 2018a (NCT, 2014a)	MOR-006 Harmatz et al., 2017 (NCT, 2016)	MOR-007 Jones et al., 2015 (NCT, 2017)
	Justification	Sources of support were fully disclosed, as were potential competing interests.	Sources of support were fully disclosed, as were potential competing interests. BioMarin Pharmaceutical Inc. provided funding for the study and for manuscript preparation.	Sources of support were fully disclosed, as were potential competing interests. BioMarin Pharmaceutical Inc. was the sponsor, and support also provided by National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA through a grant. Ismar Healthcare NV supported and manuscript development and acknowledgement of support also made to the Manchester NIHR/Wellcome Trust Clinical research facility.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; ADR, adverse drug reaction; AE, adverse event; ATS, American Thoracic Society; BL, baseline; ESA, elosulfase alfa; EXT, extension; FEV1, forced expiratory volume in 1 minute; FP, full paper; FVC, forced vital capacity; hr, hour; ITA, Italy; ITT, intention-to-treat; mITT, modified intention-to-treat; MPP, modified per protocol; MPS, mucopolysaccharidosis; MVV, maximum ventilation volume; NR, not reported; pts, patients; SAE, serious adverse event; SD, standard deviation; SE, standard error; T25FW, timed 25 foot walk test; TWN, Taiwan; tx, treatment; UK, United Kingdom; uKS, urinary keratan sulfate; UTI, urinary tract infection; USA, United States of America; wk, week; wks, weeks; yrs, years

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem.

Outcomes from included studies are summarised in Tables 34-39 below. The following table provides quick access to the relevant studies:

Study	Cross-reference
Clinical trial results	
MOR-002	**Error! Reference source not found.**
MOR-100	Table 35
MOR-004	Table 36
MOR-005	Table 37
MOR-006	Table 38
MOR-007	Table 39
Clinical trial of interest excluded in the systematic literature review	
MOR-008 (Burton et al., 2015)	Results described in section 9.8.2
Real-world evidence results	
MAA	See section 1809.6.1.2
MARS	
Real-world studies conducted in other countries	

9.6.1.1 Results from clinical trials

Table 34. Outcomes from MOR-002

Study name		**MOR-002** / NCT00884949 (NCT 2014a; Hendriksz, Santra et al, 2018a; BioMarin Pharmaceuticals, 2013 (Dose-escalation ph 1/2 study)
Size of study groups	Treatment	ESA i.v. infusion, dose escalating from 0.1 mg/kg/wk (BL-12 wks), 1.0 mg/kg/wk (wks 13-24), 2.0 mg/kg/wk(wks 25-36), then 1.0 mg/kg/wk (wks 37-72)
	Control	N/A
Study duration	Time unit	72-84 wks
Type of analysis	Intention-to - treat/per protocol	ITT+
BL 6MWT, m	n	20
	Mean (SD)	266.9 (137.39) N.B. SD 137.9 in FP
	Median	257.7
Outcome	Name	6MWT, mean change from BL in distance walked in 6 minutes (SD, n)
	Unit	Metres
Effect size	Value	Wk 12: -20.7 (85.95, 19), Wk 24: 16.3 (71.74, 17), Wk 36: 13.8 (63.25, 17), Wk 48: -4.8 (64.70), Wk 72: 4.0 (87.24, 17)
	95% CI	NR
Statistical test	Type	NR
	p value	NR
BL 3MSCT, stairs per minute	n	20

	Mean (SD)	38.9 (25.39)
	Median	32.6
Other outcome	Name	3MSCT, mean change from BL rate (SD, n)
	Unit	Stairs per minute
Effect size	Value	Wk 12: 0.3 (14.07, 19); Wk 24: 6.1 (8.66, 17), Wk 36: 7.8 (13.69, 17), Wk 48: 9.7 (14.42, 17), Wk 72: 9.7 (13.91, 17)
	95% CI	NR
Statistical test	Type	NR
	p value	NR
BL norm uKS, microg/mg	n	20
	Mean (SD)	NR
	Median	NR
Other outcome	Name	Norm uKS, mean % change from BL (SD, n)
	Unit	N/A (%)
Effect size	Value	Wk 12: -23.2% (19.04%, 19), Wk 24: -27.9% (17.92, 18), Wk 36: -40.6% (20.16%, 18), Wk 72: -32.2% (17.10, 17)
	95% CI	NR
Statistical test	Type	NR
	p value	NR

FVC BL	n	
	Mean (SD)	
	Median	
Outcome	Name	FVC, mean % change from BL (SD, n)
	Unit	N/A (%)
Effect size	Value	Wk 12: 3.4% (10.85%, 18), Wk 24: 0.2% (16.60%, 16), Wk 36: 10.7% (20.82%, 16), Wk 72: 12.5% (14.88%, 16)
	95% CI	NR
Statistical test	Type	NR
	p value	NR
FEV1 BL	n	20
	Mean (SD)	NR
	Median	NR
Other outcome	Name	FEV1, mean % change from BL (SD, n)
	Unit	N/A (%)
Effect size	Value	Wk 24 -1.8% (15.42%, NR), Wk 72: 8.4% (16.22%, NR)
	95% CI	NR
Statistical test	Type	NR

	p value	NR
MVV BL	n	20
	Mean (SD)	NR
	Median	NR
Other outcome	Name	MVV, mean % change from BL (SD, n)
	Unit	N/A (%)
Effect size	Value	Wk 12: 9.9% (21.29%, 14), Wk 24: 11.0% (21.48%, 13), Wk 36: 10.5% (17.43%, 14), Wk 72: 18.4% (20.77%, 14)
	95% CI	NR
Statistical test	Type	NR
	p value	NR
Comments		Since tx exposure differed in pts entering MOR-100 (different durations in MOR-002), LS outcomes by tx duration estimated. Overall trend in mixed model LS mean 6MWT 3 monthly of MOR-002 and MOR-100 showed no sig trend toward decline (LS mean distance remained at approx. 270m). LS mean rate for 3MSCT approx. 37 stairs/min, with no declining trend (over 5 yrs of MOR-002 and MOR-100) HAQ also reported, and FIVC. All respiratory function improved vs BL except FEV1 at Wk 24

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BL, baseline; CI, confidence interval; FP, full paper; i.v., intravenous; LS, least squares; N.B. Notez bien; norm, normalised; pts, patients; SD, standard deviation; tx, treatment; uKS, urinary keratan sulphate; wk, week; wks, weeks; yrs, years
+ ITT population was all pts enrolled, including 2 pts unable to perform 6MWT at BL or during tx

Table 35. Outcomes from MOR-100

Study name		**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002	**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002
Size of study groups	Treatment	ESA i.v. infusion, 2.0 mg/kg/wk	ESA i.v. infusion, 2.0 mg/kg/wk
	Control	N/A	N/A
Study duration	Time unit	192 wks after completing MOR-002 **Data-cut below is 19-Jul-2012**	192 wks after completing MOR-002 **Data below from NCT registry record, last updated 30-Sep-2015**
Type of analysis	Intention-to - treat/per protocol	ITT	ITT
BL 6MWT, m	n	17	16
	Mean (SD)	251.2 (116.86)	NR
	Median	256	NR
Outcome	Name	6MWT, mean change from MOR-002 BL in distance walked in 6 minutes (SD, n)	6MWT, mean change from MOR-002 BL in distance walked in 6 minutes (SD, n)
	Unit	Metres	Metres
Effect size	Value	MOR-100 BL: 15.6 (88.84, 17), MOR-100 Wk 12: 14.5 (94.69, 17), MOR-100 Wk 24: 24.5 (101.23), MOR-100 Wk 36 27.2 (62.51), MOR-100 Wk 48 6.8 (98.66), MOR-100 Wk 60 3.4 (93.24), MOR-100 Wk 72 -52.7 (133.78), MOR-100 Wk 84 13.9 (116.44, 8)	MOR-100 BL: 15.7 (89.00, 16), MOR-100 Wk 24: 24.5 (101.23, 16), MOR-100 Wk 48: 6.8 (98.66, 16), MOR-100 Wk 72: -49.8 (132.63, 17), MOR-100 Wk 96: 11.2 (85.24, 16), MOR-100 Wk 120: 4.2 (94.09, 16), MOR-100 Wk 144: 3.1 (106.82, 13); MOR-100 Wk 192: -37.1 (103.96, 9)
	95% CI	NR	NR
Statistical test	Type	NR	NR

Study name		**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002	**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002
	p value	NR	NR
BL 3MSCT, stairs per minute	n	17	16
	Mean (SD)	38.9 (25.39)	NR
	Median	NR	NR
Other outcome	Name	3MSCT, mean change from BL rate (SD, n)	3MSCT, mean change from BL rate (SD, n)
	Unit	Stairs per minute	Stairs per minute
Effect size	Value	MOR-100 BL: 12.7 (13.96, 17), MOR-100 Wk 12: 12.9 (14.51), MOR-100 Wk 24: 13.4 (17.07), MOR-100 Wk 36 9.6 (19.63), MOR-100 Wk 48 6.6 (16.87), MOR-100 Wk 60 7.9 (17.30), MOR-100 Wk 72 -3.3 (21.97), MOR-100 Wk 84 12.3 (20.59, 8)	MOR-100 BL: 12.7 (13.96, 16), MOR-100 Wk 24: 13.4 (17.07, 16), MOR-100 Wk 48: 6.6 (16.87, 16), MOR-100 Wk 72: -1.4 (21.11, 16), MOR-100 Wk 96: 9.9 (18.84, 16), MOR-100 Wk 120: 6.2 (14.41, 16), MOR-100 Wk 144: 5.4 (11.93, 12), MOR-100 Wk 192: -0.2 (10.34, 7)
	95% CI	NR	NR
Statistical test	Type	NR	NR
	p value	NR	NR
BL norm uKS, microg/mg	n	17	17
	Mean (SD)	26.9 (12.72)	NR
	Median	NR	NR
Other outcome	Name	Norm uKS, mean % change from BL (SD, n)	Norm uKS, mean % change from BL (SD, n)

Study name		**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002	**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002
	Unit	N/A (%)	N/A (%)
Effect size	Value	MOR-100 BL: -30.0% (19.23%, 17), MOR-100 Wk 12: -41.1% (20.72%), MOR-100 Wk 24: -43.6% (19.56%), MOR-100 Wk 36 -38.7% (25.73%), MOR-100 Wk 48 -41.9% (19.29%), MOR-100 Wk 60 -43.7 (26.92), MOR-100 Wk 72 -35.1% (38.19%), MOR-100 Wk 84: Not available at datacut	MOR-100 BL: -30.0% (19.23%, 17), MOR-100 Wk 24: -43.6% (19.56%, 17), MOR-100 Wk 48: -41.9% (19.29%, 16), MOR-100 Wk 72: -36.4% (36.70%, 12), MOR-100 Wk 96: -49.7% (19.93%, 17), MOR-100 Wk 120: -49.3% (22.29%, 16), MOR-100 Wk 144: -56.6% (19.54%, 16), MOR-100 Wk 168: -58.9% (16.02%, 15)
	95% CI	NR	NR
Statistical test	Type	NR	NR
	p value	NR	NR
FVC BL	n	17	20
	Mean (SD)	NR	NR
	Median	NR	NR
Outcome	Name	FVC, mean % change from BL (SD)	FVC, mean % change from BL (SD)
	Unit	N/A (%)	N/A (%)
Effect size	Value	MOR-100 BL: 11.8% (14.97%), MOR-100 Wk 24: 15.3% (16.31%), MOR-100 Wk 48 15.8% (16.56%), MOR-100 Wk 72 16.1% (21.96%), MOR-100 Wk 84: Not performed	MOR-100 BL: 11.8% (14.97%, 15), MOR-100 Wk 24: 15.3% (16.31%, 14), MOR-100 Wk 48: 15.8% (16.56%, 13), MOR-100 Wk 72: 16.1% (21.96%, 15), MOR-100 Wk 96: 14.8% (17.36%, 14), MOR-100 Wk 120: 22.8% (21.14%, 16), MOR-100 Wk 144: 17.5% (24.32%, 12), MOR-100 Wk 192: 18.6% (30.98%, 7)

Study name		**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002	**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002
	95% CI	NR	NR
Statistical test	Type	NR	NR
	p value	NR	NR
FEV1 BL	n	NR	NR
	Mean (SD)	NR	NR
	Median	NR	NR
Other outcome	Name	NR	NR
	Unit	NR	NR
Effect size	Value	NR	NR
	95% CI	NR	NR
Statistical test	Type	NR	NR
	p value	NR	NR
MVV BL	n	17	20
	Mean (SD)	NR	NR
	Median	NR	NR

Study name		**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002	**MOR-100** / NCT01242111 (NCT, 2015; Euctr GB, 2010; Hendriksz, Santra et al., 2018a; Hendriksz, Vellodi et al., 2013b; BioMarin Pharmaceuticals, 2013) EXT of ph 1/2 MOR-002
Other outcome	Name	MVV, mean % change from BL (SD)	MVV, mean % change from BL (SD, n)
	Unit	N/A (%)	N/A (%)
Effect size	Value	MOR-100 BL: 11.1% (16.44%), MOR-100 Wk 24: 9.8% (22.25%), MOR-100 Wk 48 3.5% (17.78%), MOR-100 Wk 72 10.1% (27.83%), MOR-100 Wk 84: Not performed	MOR-100 BL: 11.1% (16.44%, 13), MOR-100 Wk 24: 9.8% (22.25%, 13), MOR-100 Wk 48 3.5% (17.78%, 12), MOR-100 Wk 72: 10.1% (27.83%, 13), MOR-100 Wk 96: -4.9% (35.53%, 12), MOR-100 Wk 120: -3.3% (28.35%, 13), MOR-100 Wk 144: -3.5% (34.61%, 11), MOR-100 Wk 192: 28.2% (38.78%, 6)
	95% CI	NR	NR
Statistical test	Type	NR	NR
	p value	NR	NR
Comments		Since tx exposure differed in pts entering MOR-100 (different durations in MOR-002), LS outcomes by tx duration estimated. Overall trend in mixed model LS mean uKS over 3 months MOR-002 and MOR-100 was a declining trend. Decline at Wk 72 in 6MWT and 3MSCT mainly due to 4 pts having orthopedic surgery within 4 wks of Wk 72. Overall 6MWT increased during MOR-100. uKS reduced similarly in MOR-100 as in MOR-002 during weeks at 2.0 mg/kg/wk MVV improvement in MOR-002 Wk 24 was sustained through to MOR-100 Wk 72. FVC continued to improve to MOR-100 Wk 24 and was then sustained through to Wk 72.	N.B. Later datacut in this column

Abbreviations: Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BL, baseline; CI, confidence interval; ESA, elosulfase alfa; FVC, forced vital capacity; ITT, intention-to-treat; i.v., intravenous; MVV, maximum ventilation volume; N.B., notez bien; ph, phase; pts, patients; qw, weekly; SD, standard deviation; tx, treatment; uKS, urinary keratan sulphate; wk, week; wks, weeks;

Table 36. Outcomes from MOR-004

Study name		**MOR-004** ph 3 RCT (NCT, 2014b; Hendriksz, Burton et al., 2014b; Hendriksz, Guigliani et al., 2015d)
Size of study groups	Treatment	ESA i.v. infusion, 2.0 mg/kg/wk (n=58) ESA i.v. infusion, 2.0 mg/kg qow (n=59)
	Control	PLA (n=59)
Study duration	Time unit	24 wks
Type of analysis	Intention-to -treat/per protocol	**ITT**
BL 6MWT, m	n	177 randomised, 176 treated
	Mean (SD)	ESA 2.0mg/kg/wk: 203.9 (76.32) ESA 2.0mg/kg qow: 205.7 (81.19) PLA: 211.9 (69.88)
	Median	ESA 2.0mg/kg/wk: 216.5 ESA 2.0mg/kg qow: 218.0 PLA: 228.9
Outcome	Name	6MWT, LS mean difference in change from BL in distance walked in 6 minutes (SD, n), 1ry endpoint
	Unit	Metres
Effect size	Value	Wk 24 ESA 2.0mg/kg/wk vs PLA: 23.0m (observed mean), 22.5 (model-based mean)
	95% CI	qw vs PLA: 2.9, 43.1 (around mean) qw vs PLA: 4.0, 40.9 (around model-based mean)
Statistical test	Type	t test from ANCOVA model adjusted for BL covariates (age group and 6MWT category)
	p value	qw vs PLA: 0.0174 (based on model-based mean difference)

Study name		**MOR-004** ph 3 RCT (NCT, 2014b; Hendriksz, Burton et al., 2014b; Hendriksz, Guigliani et al., 2015d)
BL 3MSCT, stairs per minute	n	ESA 2.0mg/kg/wk: 58 ESA 2.0mg/kg qow: 59 PLA: 59
	Mean (SD)	ESA 2.0mg/kg/wk: 29.6 (16.44) ESA 2.0mg/kg qow: 27.1 (15.80) PLA: 30.0 (14.05)
	Median	ESA 2.0mg/kg/wk: 30.5 ESA 2.0mg/kg qow: 25.5 PLA: 30.8
Other outcome	Name	3MSCT, LS mean difference in change from BL rate (SD, n)
	Unit	Stairs per minute
Effect size	Value	Wk 24 ESA 2.0mg/kg/wk vs PLA: 1.1 stairs/min Wk 24 ESA 2.0mg/kg qow vs PLA: -0.5 stairs/min
	95% CI	qw vs PLA:-1.9, 4.2 (around observed mean) qw vs PLA:-2.1, 4.4 (around model-based mean)
Statistical test	Type	t test from ANCOVA model adjusted for BL covariates (age group, 6MWT category and continuous 3MSCT)
	p value	qw vs PLA: 0.4935 (NS) based on model-based mean difference
BL norm uKS, microg/mg	n	ESA 2.0mg/kg/wk: 58 ESA 2.0mg/kg qow: 59 PLA: 58
	Mean (SD)	ESA 2.0mg/kg/wk: 26.9 (14.11) ESA 2.0mg/kg qow: 28.6 (21.17) PLA: 25.7 (15.09)
	Median	ESA 2.0mg/kg/wk: 24.1 ESA 2.0mg/kg qow: 27.4 PLA: 26.7
Other outcome	Name	Norm uKS, LS mean difference in % change from BL (SD, n)

Study name		**MOR-004** ph 3 RCT (NCT, 2014b; Hendriksz, Burton et al., 2014b; Hendriksz, Guigliani et al., 2015d)
	Unit	N/A (%)
Effect size	Value	Wk 24 ESA 2.0mg/kg/wk vs PLA: -40.7% Wk 24 ESA 2.0mg/kg qow vs PLA: -30.2%
	95% CI	qw vs PLA: -49.7, -31.6 (around observed mean) qw vs PLA: -49.0, -32.4 (around model-based mean)
Statistical test	Type	NR
	p value	qw vs PLA: <0.0001 based on model-based mean difference
FVC BL	n	ESA 2.0 mg/kg/wk n=58 ESA 2.0 mg/kg qow n=59 PLA n=59
	Mean (SD)	
	Median	
Outcome	Name	FVC, LS mean difference in % change from BL (SD, n)
	Unit	N/A (%)
Effect size	Value	ESA 2.0mg/kg/wk vs PLA: 3.3
	95% CI	qw vs PLA: -3.1, 9.6 (around model-based mean)
Statistical test	Type	NR
	p value	NR
FEV1 BL	n	ESA 2.0 mg/kg/wk n=58 ESA 2.0 mg/kg qow n=59 PLA n=59

Study name		**MOR-004** ph 3 RCT (NCT, 2014b; Hendriksz, Burton et al., 2014b; Hendriksz, Guigliani et al., 2015d)
	Mean (SD)	
	Median	
Other outcome	Name	MVV, LS mean difference in % change from BL (SD, n)
	Unit	N/A (%)
Effect size	Value	ESA 2.0mg/kg/wk vs PLA: 10.3
	95% CI	qw vs PLA: -1.8, 22.4 (around model-based mean)
Statistical test	Type	NR
	p value	NR
MVV BL	n	ESA 2.0 mg/kg/wk n=58 ESA 2.0 mg/kg qow n=59 PLA n=59
	Mean (SD)	
	Median	
Other outcome	Name	MVV, LS mean difference in % change from BL (SD, n)
	Unit	N/A (%)
Effect size	Value	ESA 2.0mg/kg/wk vs PLA: 10.3
	95% CI	qw vs PLA: -1.8, 22.4 (around model-based mean)
Statistical test	Type	NR

Study name		**MOR-004** ph 3 RCT (NCT, 2014b; Hendriksz, Burton et al., 2014b; Hendriksz, Guigliani et al., 2015d)
	p value	NR
Comments		2 missing 6MWT values were imputed using multiple imputation. Over 99% of subjects completed study. QOW dosage resulted in 6MWT results similar to PLA. Improvement of 6MWT signficant from 12 wks. 3MSCT results not significant - not known why they didn't mirror 6MWT results, except less experience with this test and pts have difficulty climbing stairs due to severe skeletal impairments. 6MWT/3MSCT/MVV composite z-score change from BL LS mean difference (95% CI) 0.1 (-0.0, 0.3) Rapid and sustained reduction in uKS in both tx arms. MPS HAQ also reported.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; ESA, elosulfase alfa; FVC, forced vital capacity; HAQ, health assessment questionnaire; ITT, intention-to-treat; LS, least squares; MVV, maximum ventilation volume; NS, not (statistically) significant; ph, phase; PLA, placebo; pts, patients; qow, every other week; qw, weekly; RCT, randomised controlled trial; SD, standard deviation; tx, treatment; uKS, urinary keratan sulphate; wk, week; yrs, years

Table 37. Outcomes from MOR-005

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
Size of study groups	Treatment	ESA QOW-QOW (n=59) ESA QW-QW (n=56)	ESA QW-QW (n=43)
	Control	PLA-QOW (n=29) PLA-QW (n=29) MorCAP 1 (N=97)	MorCAP2 (N=79)
Study duration	Time unit	120 wks (from MOR-004 BL)	120 wks (from MOR-004 BL)

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
Type of analysis	Intention-to -treat/per protocol	**ITT**	**MPP**
BL 6MWT, m	n	PLA-QOW (n=29) PLA-QW (n=29) ESA QOW-QOW (n=59) ESA QW-QW (n=56) MorCAP1 (n=97)	ESA QW-QW (n=43) MorCAP2 (n=79)
	Mean (SD)	PLA-QOW 219.7 (74.2) PLA-QW 207.2 (64.9) ESA QOW-QOW 205.7 (81.2) ESA QW-QW 209.4 (71.8) MorCAP1 207.8 (84.3)	ESA QW-QW 208.8 (73.2) MorCAP2 210.4 (83.4)
	Median	PLA-QOW 239.5 PLA-QW 217.2 ESA QOW-QOW 218.0 ESA QW-QW 218.7 MorCAP1 220.5	ESA QW-QW 226.9 MorCAP2 221.5
Outcome	Name	6MWT Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 1 = 72 wk) Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 2 = 120 wks)	6MWT Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 1 = 72 wk) Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 2 = 120 wks)
	Unit	Metres	Metres
Effect size	Value	QW-QW Wk 24: 37.2 [7.9] Wk 36: 42.2 [7.1] Wk 72: 30.7 [10.2] / 31.8 [10.86] N=54 Wk 120: 32.0 [11.3] / 32.1 [11.75] N=51 MorCAP	QW-QW (MPP) Wk 24: 41.5 [9.1] Wk 36: 44.4 [8.3] Wk 72: 37.5 [11.0] / 38.5 [11.02] N=43 (Yr 1) Wk 120: 39.9 [10.1] / 39.0 [11.32] N=41 MorCAP2

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
		Wk 72/Yr 1: NR / -8.4 [8.91], N=80 Wk 120/Yr 2: NR / -16.4 [12.50], N=40	Wk 72: NR / -6.7 [8.78] N=67 Wk 120: NR / -21.9 [12.30] N=27
	95% CI	NR	NR
Statistical test	Type	t-test and repeated measures ANCOVA model comparing treated QW-QW vs untreated (MorCAP 1) pts	t-test and repeated measures ANCOVA model comparing treated QW-QW vs untreated (MorCAP 2) pts
	p value	Wk 72/Yr 1: 0.0046 (vs MorCAP1) Wk 120/Yr 2: 0.0050 (vs MorCAP1)	Wk 72/Yr 1: 0.0016 (vs MorCAP2) Wk 120/Yr 2: 0.0003 (vs MorCAP2)
BL 3MSCT, stairs per minute	n	PLA-QOW (n=29) PLA-QW (n=29) ESA QOW-QOW (n=59) ESA QW-QW (n=56) MorCAP1 (n=88)	ESA QW-QW 43 MorCAP2 74
	Mean (SD)	PLA-QOW 33.1 (15.6) PLA-QW 26.9 (12.1) ESA QOW-QOW 27.1 (15.8) ESA QW-QW 30.1 (16.2) MorCAP1 31.3 (17.5)	ESA QW-QW 31.3 (16.2) MorCAP2 32.2 (17.8)
	Median	PLA-QOW 33.0 PLA-QW 29.0 ESA QOW-QOW 25.5 ESA QW-QW 30.7 MorCAP1: 29.3	ESA QW-QW 31.3 MorCAP2 30.6
Other outcome	Name	3MWT Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 1 = 72 wk) Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 2 = 120 wks)	3MWT Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 1 = 72 wk) Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 2 = 120 wks)
	Unit	Stairs per minute	Stairs per minute

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
Effect size	Value	QW-QW Wk 72: NR / 5.0 [1.71] N=54 Wk 120: NR / 5.3 [2.10] N=51 MorCAP Wk 72/Yr 1: NR / -0.7 [1.46], N=80 Wk 120/Yr 2: NR / -1.1 [2.27], N=40	QW-QW Wk 72: NR / 5.5 [1.85] N=43 Wk 120: NR / 6.2 [2.24] N=41 MorCAP Wk 72/Yr 1: NR / 0.5 [1.51], N=67 Wk 120/Yr 2: NR / -1.2 [2.39], N=27
	95% CI	NR	NR
Statistical test	Type	t-test and repeated measures ANCOVA model comparing treated QW-QW vs untreated (MorCAP 1) pts	t-test and repeated measures ANCOVA model comparing treated QW-QW vs untreated (MorCAP 2) pts
	p value	Wk 72/Yr 1: 0.0129 (vs MorCAP1) Wk 120/Yr 2: 0.0407 (vs MorCAP1)	Wk 72/Yr 1: 0.0375 (vs MorCAP2) Wk 120/Yr 2: 0.0236 (vs MorCAP2)
BL norm uKS, microg/mg	n	PLA-QOW (n=28) PLA-QW (n=29) ESA QOW-QOW (n=59) ESA QW-QW (n=56) MorCAP1 (n=97)	ESA QW-QW 43 MorCAP2 79
	Mean (SD)	PLA-QOW 22.7 (15.3) PLA-QW 28.5 (14.9) ESA QOW-QOW 28.6 (21.2) ESA QW-QW 27.2 (14.2) MorCAP1 33.5 (25.6)	ESA QW-QW 24.9 (13.1) MorCAP2 32.2 (27.4)
	Median	PLA-QOW 25.0 PLA-QW 30.3 ESA QOW-QOW 27.4 ESA QW-QW 25.0 MorCAP1 30.7	ESA QW-QW 23.4 MorCAP2 27.6
Other outcome	Name	Norm uKS Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 1 = 72 wk) Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 2 = 120 wks)	Norm uKS Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 1 = 72 wk) Mean [SE] change from MOR-004 BL / LS mean change from BL (Yr 2 = 120 wks)

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
	Unit	%	%
Effect size	Value	QW-QW Wk 72: NR / -57.6 [9.06] N=51 Wk 120: NR / -63.8 [6.60] N=47 MorCAP Wk 72/Yr 1: NR / 32.7 [7.64], N=72 Wk 120/Yr 2: NR / 5.6 [6.98], N=23	QW-QW Wk 72: NR / -57.5 [11.16] N=41 Wk 120: NR / -63.8 [7.47] N=38 MorCAP Wk 72/Yr 1: NR / 29.6 [9.30], N=59 Wk 120/Yr 2: NR / 6.2 [8.46], N=13
	95% CI	NR	NR
Statistical test	Type	t-test and repeated measures ANCOVA model comparing treated QW-QW vs untreated (MorCAP 1) pts	t-test and repeated measures ANCOVA model comparing treated QW-QW vs untreated (MorCAP 2) pts
	p value	Wk 72/Yr 1: <0.0001 (vs MorCAP1) Wk 120/Yr 2: <0.0001 (vs MorCAP1)	Wk 72/Yr 1: <0.0001 (vs MorCAP2) Wk 120/Yr 2: <0.0001 (vs MorCAP2)
FVC BL	n	162	MOR-005 pts 118 MorCAP pts 75
	Mean (SD)	1.1 (0.7)	MOR-005 pts 1.1 (0.8) MorCAP pts 1.1 (0.7)
	Median	NR	NR
Outcome	Name	FVC, Mean [SE] change from BL	FVC MOR-005 pts: Mean [SE] change from BL / LS mean (%) change from MOR-004 BL MorCAP pts: Mean (SD), N / LS mean (%) change from BL
	Unit	Litres	Litres

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
Effect size	Value	Wk 24: 0.025 [0.009] Wk 72: 0.054 [0.012] Wk 120: 0.076 [0.018]	MOR-005 pts Wk 24:0.024 [0.011] Wk 72: 0.062 [0.012] / +0.0589 (7.6%) Wk 120: 0.087 [0.021] / +0.0827 (8.8%) MorCAP pts Yr 1: 1.2 (0.7), N=60 / +0.0008 (2.2%) Yr 2: 1.2 (0.7), N=23 / -0.0299 (2.6%)
	95% CI	NR	NR
Statistical test	Type	NR	ANCOVA analysis comparing LS mean changes from BL between MOR-005 pts and Mor-CAP pts
	p value	NR	Yr 1: 0.0279 Yr 2: 0.0429
FEV1 BL	n	161	MOR-005 pts 118 MorCAP pts 74
	Mean (SD)	0.9 (0.6)	MOR-005 pts 1.0 (0.6) MorCAP pts 1.0 (0.6)
	Median	NR	NR
Other outcome	Name	FEV1, Mean [SE] change from BL	FEV1 MOR-005 pts: Mean [SE] change from BL / LS mean (%) change from MOR-004 BL MorCAP pts: Mean (SD), N / LS mean (%) change from BL
	Unit	Litres	Litres

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
Effect size	Value	Wk 24: 0.019 [0.009] Wk 72: 0.039 [0.011] Wk 120: 0.053 [0.017]	MOR-005 pts Wk 24: 0.017 [0.011] Wk 72: 0.044 [0.011] / +0.0385 (6.3%) Wk 120: 0.065 [0.019] / +0.06 (8.5%) MorCAP pts Yr 1: 1.0 (0.7), N=60 / -0.0399 (0.9%) Yr 2: 1.1 (0.5), N=21 / -0.052 (-0.6%)
	95% CI	NR	NR
Statistical test	Type	NR	ANCOVA analysis comparing LS mean changes from BL between MOR-005 pts and Mor-CAP pts
	p value	NR	Yr 1: 0.0079 Yr 2: 0.0339
MVV BL	n	153	MOR-005 pts 112 MorCAP pts 69
	Mean (SD)	31.9 (21.8)	MOR-005 pts 34.3 (23.5) MorCAP pts 31.7 (17.7)
	Median	NR	NR
Other outcome	Name	MVV, Mean [SE] change from BL	MVV MOR-005 pts: Mean [SE] change from BL / LS mean (%) change from MOR-004 BL MorCAP pts: Mean (SD), N / LS mean (%) change from BL
	Unit	Litres/minute	Litres/minute

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
Effect size	Value	Wk 24: 1.38 [0.60] Wk 72: 1.78 [0.74] Wk 120: 1.80 [1.04]	MOR-005 pts Wk 24: 1.54 [0.75] Wk 72: 1.77 [0.89] / +1.7 (9.6%) Wk 120: 1.84 [1.21] / +2.1 (7.3%) MorCAP pts Yr 1: 33.6 (19.1), N=52 / -2.4 (0.8%) Yr 2: 32.7 (16.3), N=21 / -5.2% (-7.0%)
	95% CI	NR	NR
Statistical test	Type	NR	ANCOVA analysis comparing LS mean changes from BL between MOR-005 pts and Mor-CAP pts
	p value	NR	Yr 1: 0.0221 Yr 2: 0.0127
Comments		Cohorts other than the optimal dosing regimen of QW-QW did not result in consistent improvement in 6MWT. Randomization of PLA group to QW and QOW was not stratified by age or BL endurance and resulted in imbalanced groups. For 6MWT and 3MSCT model-based ANCOVA shows sig diff in change from BL for treated (QW-QW ITT) vs untreated (MorCAP) pts. Age and walking ability did not impact on improvements seen during the study in 6MWT results. uKS showed continued gradual decline in MOR-005 and reductions were seen irrespective of age cohort [data not shown]. For uKS model-based ANCOVA shows highly sig diff (p<0.0001) in change from BL for treated (QW-QW ITT) vs untreated (MorCAP) pts.	MPP population excluded non-compliant pts and those who underwent orthopedic surgery. For 6MWT and 3MSCT model-based ANCOVA shows sig diff in change from BL for treated (QW-QW MPP) vs untreated (MorCAP) pts. For uKS model-based ANCOVA shows highly sig diff (p<0.0001) in change from BL for treated (QW-QW MPP) vs untreated (MorCAP) pts. BL data from Suppl. 1. Groups had similar BL characteristics. In MPP population (on ESA), FVC, FEV1 and MVV mean increases were 9.2%, 8.8% and 6.1%, respectively after 120 wks. In pt <=14 yrs age group, treated and untreated pts improved, presumably due to growth (but treated pts improved more). After the age of 14 MPS pts have limited growth. In pts >14 yrs respiratory

Study name		**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)	**MOR-005** ph 3 EXT (Hendriksz, Parini et al., 2016c)
		MVV improved to Wk 72 then stabilized. FVC and FEV1 increased continuously over 120 wk study period. Mean follow-up time in MorCAP was 63.7 wks for Yr 1 and 107 wks for Yr 2. These were compared to 72 wk and 120 wk times of MOR-004/005. BL data from Suppl. 1.	function improved in treated pts, but deteriorated in untreated pts.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; ESA, elosulfase alfa; FEV1, forced expiratory volume in 1 minute; FVC, forced vital capacity; ITT, intention-to-treat; LS, least squares; MPP, modified per protocol; MVV, maximum ventilation volume; pts, patients; qow, every other week; qw, weekly; SD, standard deviation; SE, standard error; suppl., supplement; tx, treatment; uKS, urinary keratan sulphate; wk, week; wks, weeks; yr, year; yrs, years

Table 38. Outcomes from MOR-006

Study name		**MOR-006** ph 2 OL (NCT, 2016; Harmatz et al., 2017) Pts with limited ambulation (>=5 unable to walk >=30m in 6MWT)	**MOR-006** ph 2 OL (NCT, 2016; Harmatz et al., 2017) Pts with limited ambulation (>=5 unable to walk >=30m in 6MWT)
Size of study groups	Treatment	ESA 2.0 mg/kg/wk (N=16 enrolled, N=15 received study drug)	ESA 2.0 mg/kg/wk (N=16 enrolled, N=15 received study drug)
	Control	N/A	N/A
Study duration	Time unit	Initial ph 48 wks. EXT ph additional 96 wks. Total: 144 wks	Initial ph 48 wks. EXT ph additional 96 wks. Total: 144 wks
Type of analysis	Intention-to -treat/per protocol	**mITT** (randomised and received at least one dose of study drug), N=15	**MPP** (pts completing and not missing 20% or more of infusions from BL to 48 wks, N=10
BL norm uKS, microg/mg	n	15	15
	Mean (SD)	NR	NR

	Median	NR	NR
Other outcome	Name	Norm uKS % change from BL, mean (SD)	Norm uKS % change from BL, mean [SE]
	Unit	N/A	N/A
Effect size	Value	Wk 24: -47.7% (15.40%) Wk 48: -43.4% (24.82%) Wk 72: -45.5% (19.67%) Wk 96: -48.3% (24.13%)	Wk 48: -52.4% [3.8%]
	95% CI	NR	NR
Statistical test	Type	NR	NR
	p value	NR	NR
FVC BL	n		8
	Mean (SD)		0.66 [SE 0.06]
	Median		NR
Outcome	Name		FVC Wk 48 mean [SE], N / Wk 48 mean change [SE], N
	Unit		Litres
Effect size	Value		0.56 [0.05], 9 / -0.07 [0.08], 8
	95% CI		NR
Statistical test	Type		NR
	p value		NR

FEV1 BL	n	8
	Mean (SD)	0.49 [SE 0.02]
	Median	NR
Other outcome	Name	FEV1 Wk 48 mean [SE], N / Wk 48 mean change [SE], N
	Unit	Litres
Effect size	Value	0.48 [0.04], 9 / 0.01 [0.03], 8
	95% CI	NR
Statistical test	Type	NR
	p value	NR
MVV BL	n	9
	Mean (SD)	15.35 [SE 1.3]
	Median	NR
Other outcome	Name	MVV Wk 48 mean [SE], N / Wk 48 mean change [SE], N
	Unit	Litres/minute
Effect size	Value	17.94 [1.5], 9 / 2.59 [0.67], 9
	95% CI	NR
Statistical test	Type	NR

p value		NR
Comments	1ry outcomes reported in MOR-006 were 25FWT, GPT and FDT. uKS was a 2ry outcome (up to 96 weeks).	Respiratory function in these MPP population pts was poor compared to MorCAP pts (N=325): mean FVC 0.66 at BL in MOR-006 vs 1.1L in pts up to 18 yrs old in MorCAP and 1.5L in pts >18 yrs in MorCAP. Mean MVV was 15.35 L/min in MOR-006 vs 32.4 L/min in MorCAP pts up to 18 yrs and 42.1 L/min in adults >18 yrs. Over the 48 wks, FVC and FEV1 remained relatively stable and MVV increased somewhat.

Abbreviations: 1ry, primary; 2ry, secondary; 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BL, baseline; CI, confidence interval; ESA, elosulfase alfa; EXT, extension; FVC, forced vital capacity; ITT, intention-to-treat; i.v., intravenous; L, litres; LS, least squares; m, metres; mITT, modified intention-to-treat; MPP, modified per protocol; MVV, maximum ventilation volume; norm, normalized; OL, open-label; ph, phase; PLA, placebo; pts, patients; qw, weekly; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; tx, treatment; uKS, urinary keratan sulphate; wk, week; yrs, years

Table 39. Outcomes from MOR-007

Study name		**MOR-007** (NCT, 2017; Jones et al., 2015) Pts <5 yrs
Size of study groups	Treatment	ESA 2.0 mg/kg/wk (N=15)
	Control	N/A
Study duration	Time unit	52 wks initial tx phase (reported here) Up to 156 wk EXT phase + 1 wk for final study assessments
Type of analysis	Intention-to -treat/per protocol	Efficacy analysis set (≥1 dose of study drug and had ≥1 postbaseline efficacy measurement)
BL norm uKS, microg/mg	n	15
	Mean (SD)	35.9 (12.32)

Study name		**MOR-007** (NCT, 2017; Jones et al., 2015) Pts <5 yrs
	Median	35.4
Other outcome	Name	Norm uKS % change from BL, mean (SD)
	Unit	N/A
Effect size	Value	Wk 2: -30.2% (12.7%) Wk 52: -43.5% (22.2%) in Jones 2017 Wk 52: -44.3% (21.15%) in registry (N=11)
	95% CI	NR
Statistical test	Type	NR
	p value	NR
Comments		Early intervention with ESA decreases uKS. Normalized uKS levels in healthy controls aged 0-6 yrs range between 0.42 and 5.7 µg/mg creatinine. So, BL level in MPS IVA pts in MOR-007 is 10x above the mean for the control population. Decline in uKS of 43.5% observed here was comparable to that reported for older children and adult pts in ESA ph 1-3 studies.

Abbreviations: BL, baseline; CI, confidence interval; ESA, elosulfase alfa; ph, phase; pts, patients; SD, standard deviation; tx, treatment; uKS, urinary keratan sulphate; wk, week

9.6.1.2 Real-world evidence

The real-world results of elosulfase alfa from the patients treated under the MAA agreement and from the multinational observational study (MARS) are presented in this section.

9.6.1.2.1 Long-term outcomes from patients initiated under the MAA in England (analysis based on latest data cut-off from November 2019)

For a reminder of the MAA methodology, patient disposition and baseline characteristics, please refer to section 9.4.

Clinical outcomes:

uKS

Mean uKS decreased rapidly and remained stable over time thereafter, regardless of treatment duration (Figure 14). In patients with both pre-treatment baseline and follow-up data:

- In treatment-naïve patients (n=[redacted]; mean treatment duration of [redacted] years), mean (SD) uKS was [redacted] ([redacted]) µg/mg creatinine at baseline and decreased to [redacted] ([redacted]) µg/mg creatinine at last follow-up;
- In ex-trial patients (n=[redacted]; mean treatment duration of [redacted] years), mean (SD) uKS was [redacted] ([redacted]) µg/mg creatinine at baseline and decreased to [redacted] ([redacted]) µg/mg creatinine at last follow-up.

Mean uKS changed statistically significantly from baseline in both groups of patients (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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Figure 15):

- In treatment-naïve patients, change was -[redacted] ([redacted]) and,
- In ex-trial patients, change was -[redacted] ([redacted]).

In addition, analysis by age group at treatment initiation showed that uKS levels were higher in patients under 18 years old, while adult patients often had normal or virtually normal baseline uKS levels (Figure 16).

Figure 14. MAA mean urinary keratan sulfate (uKS) over time

[redacted]

Figure 15. Box plot comparing uKS at pre-treatment baseline and at last follow-up among patients with both measures

[redacted]

Figure 16. Urinary keratan sulfate (uKS) over time by age at treatment initiation

Weight

Weight remained stable over time after reaching adult height (**Figure 17**). Younger patients tended to gain weight in line with growth and there was no important weight variation in adult patients.

Figure 17. MAA weight over time by age at treatment initiation

Endurance

Overall, patients showed an initial increase in 6MWT distance and a stabilisation thereafter (Figure 18). In patients with both baseline and follow-up data:

- In treatment-naïve patients (n=[redacted]; mean treatment duration of [redacted] years), mean (SD) 6MWT distance was [redacted] ([redacted]) m at baseline and increased by

additional + [redacted] m (+[redacted]%) to [redacted] ([redacted]) m at last follow-up (p=[redacted]; [redacted]% CI -[redacted], +[redacted]) (Figure 19);

- In ex-trial patients (n=[redacted]; mean treatment duration of [redacted] years), mean (SD) 6MWT distance was [redacted] ([redacted]) m at baseline and increased by additional [redacted] m to [redacted] ([redacted]) m at last follow-up (p=[redacted]; [redacted]% CI -[redacted], +[redacted]) (**Figure 19**).

All patients showed better 6MWT outcomes than those reported for untreated patients from the MOR-001 natural history study (Figure 18). Overall, patients increased in 6MWT distance in the first years of treatment and sustained the results for up to 10 years.

Figure 18. Six-minute walk test (6MWT) distance over time by trial history vs. untreated patients in the MOR-001 study

[redacted]

Figure 19. Box plot of 6MWT at baseline and at last measurement

[redacted]

Pulmonary function

Lung function (FVC and FEV1) was stable or numerically improved regardless of age at treatment initiation, particularly when compared to natural history data from the MOR-001 study (**Figure 20**). In patients with both baseline and follow-up data, the mean (SD) FVC and FEV 1 were calculated and provided in **Table 40**.

- In the age group of patients who were < 18 years old at baseline (mean treatment duration [redacted] years), the percent change from baseline to the last follow-up was +[redacted]% (+[redacted] L) for FVC (
- Figure **21**A) and +[redacted]% (+[redacted] L) for FEV1 (
- Figure **21**B);
- In the age group of patients who were ≥ 18 years old at baseline (mean treatment duration 5.9 years), the percent change from baseline to the last follow-up was -[redacted]% (-[redacted]L) for FVC (
- Figure **21**A) and +[redacted]% (+[redacted]L) for FEV1 (
- Figure **21**B).

Table 40. Mean Change baseline in FVC and FEV_1 by age group

	Patients < 18 years old	Patients ≥ 18 years old
FVC, L		
N	[redacted]	[redacted]
Mean (SD) at Baseline	[redacted] ([redacted])	[redacted] ([redacted])
Mean (SD) at Last Follow-up	[redacted] ([redacted])	[redacted] ([redacted])
Mean change, L (%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
95% Confidence Interval	[redacted], [redacted]	[redacted], [redacted]
p-value	[redacted]	[redacted]

FEV, L		
N	[redacted]	[redacted]
Mean (SD) at Baseline	[redacted] ([redacted])	[redacted] ([redacted])
Mean (SD) at Last Follow-up	[redacted] ([redacted])	[redacted] ([redacted])
Mean change, L (%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
95% Confidence Interval	[redacted], [redacted]	[redacted], [redacted]
p-value	[redacted]	[redacted]

Figure 20. Change in FVC (A) and FEV1 (B) over time with comparison to MOR-001 natural history

Figure 21. Box plots of pulmonary function (FVC [A] and FEV1 [B]) at baseline versus last follow-up stratified by age group

Left ventricular ejection fraction (LVEF)

All patients who had ejection fraction measured at baseline had normal findings, and Ejection fraction remained within the normal range during the course of the MAA (**Figure 22**).

Figure 22. Change in LVEF over time

Patient-reported outcomes (PROs):

Activities of daily living

MPS-HAQ data showed numerical improvements (i.e. decreases) across all domains – mobility, self-care, and caregiver domains – over 3 years (

Figure 23). These improvements were mainly driven by improvements in the patients initiated on treatment during the MAA period and in the subgroup of ex-trials patients who started treatment in MOR-002. Patients who started treatment in the clinical trials and had been on treatment long-term also showed trend towards stabilisation of the mean score across all domains (

Figure 24).

Comparison of MPS-HAQ data from the MAA showed improvements across all domains that are generally numerically higher than the untreated cohort from MOR-001 (**Table 41**).

Table 41. MPS-HAQ mean change baseline versus last follow-up

	Mean change from baseline (lower score is an improvement)		
	Year 1	**Year 2**	**Year 3**
Mobility domain			
ERT-Naïve Patients (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
Ex-Trial (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
MOR-002 (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
MOR-001 (Natural history cohort)	[redacted]	[redacted]	[redacted]
Self-care domain			
ERT-Naïve Patients (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
Ex-Trial (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
MOR-002 (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
MOR-001 (Natural history cohort)	[redacted]	[redacted]	[redacted]
Caregiver domain			

ERT-Naïve Patients (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
Ex-Trial (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
MOR-002 (Mean Treatment duration, [redacted] years)	[redacted]	[redacted]	[redacted]
MOR-001 (Natural history cohort)	[redacted]	[redacted]	[redacted]

Figure 23. Change from baseline in MPS-HAQ domains over 1, 2 and 3 years of the MAA

Figure 24. Change in MPS-HAQ score by domain over time

Figure 25. Patients showing stability, decline, or improvement in wheelchair status over time versus baseline (based on MPS-HAQ Mobility Q33 and Q33a regarding wheelchair se)

Other patient-reported outcomes

Overall, **QoL (the EQ-5D-5L utility score)** remained stable over time, even in patients treated for up to 10 years; patients initiating treatment in the MAA showed slight improvements from baseline (

Figure 26 and Figure 27).

Pain severity scores remained relatively stable over time. Improvements over time in pain severity were mainly seen in younger patients (completing the APPT), while adults (completing the BPI) overall showed no substantial change (Figure 28).

[redacted] depressive symptoms as assessed with the BDI (Figure 29).

Given that these assessments were first performed at enrolment in the MAA in all subjects, which means that subjects previously enrolled in clinical trials had been on treatment for several years at the time of baseline assessment, this may explain the relatively good baseline scores and stable follow-up scores in most of these patients.

Figure 26. Change from baseline in EQ-5D-5L utility score over time in all patients and by trial history

Figure 27. Change from baseline in EQ-5D-5L utility score over time

Figure 28. Pain severity as assessed with the Adolescent Paediatric Pain Tool (APPT; patients aged <18 years) (A) and Brief Pain Inventory (BPI; patients aged ≥18 years) (B) over time by trial history

Figure 29. Beck Depression Inventory (BDI) score* change from baseline over time

Further published evidence on the MAA:

Data as of March 2018 were reported for patients with at least 24 months follow-up from the MAA baseline by Adam et al. 2019a and Hughes et al. 2019 (Hughes et al., 2019b, Adam et al., 2019a), showing that QoL/ADL were stable over time.

As of March 2018, clinical trial patients (n=26 overall) had mean (SD) treatment duration of 7 (1.4) years, whereas new MAA patients (n=10 overall) had mean (SD) treatment duration of 2.1 (0.3) years.

For ex-trial patients, mean EQ-5D-5L change from baseline after 24 months was -0.04 (SD 0.29) in 22 patients and mean MPS-HAQ CD change from baseline was 0.38 (SD 6.27) in 24 patients; mean EQ-5D-5L change from baseline to 24 months in patients starting elosulfase alfa during the MAA was 0.08 (SD 0.53) in 8 patients and mean MPS-HAQ CD change from baseline was -1.3 (SD 16.79) in 10 MAA patients.

Baseline to 20-month data were reported for the Beck Depression Inventory (BDI) and baseline to 24-month data for the Adolescent and Pediatric Pain Tool (APPT) (Adam et al., 2019a); BDI was unchanged in patients initiating elosulfase alfa in clinical trial, with change from baseline -0.47 (SD 2.34) in 19 patients, and improved in 4 patients initiating elosulfase alfa in the MAA (change from BL -5.75 (SD 6.85)) (Hughes et al., 2019b); APPT showed

improved change from baseline, -3.27 (SD 1.62) in 11 clinical trial patients, and -2.33 (SD 2.83) in 9 MAA patients.

Brief Pain Inventory (BPI) data were assessed in 6 clinical trial patients (change from BL unchanged, -0.17 (SD 2.23) (Adam et al., 2019a).

No patients discontinued treatment due to intolerability or lack of efficacy (Adam et al., 2019a).

Mukherjee et al (Mukherjee et al., 2020, Mukherjee et al., 2019a) also reported endurance outcomes from the English MAA, with data-cut off from January 2019, demonstrating that all patients met the criteria for continuing treatment under the MAA, i.e. that improvement or stabilisation in at least four out of 5 clinical or PRO outcomes was achieved.

Patients initiated during the MAA period (n=21 overall) had mean (SD) treatment duration of 2.7 (0.2) years, whereas ex-trial patients (n=26 overall) had mean (SD) treatment duration of 7.5 (1.9) years:

In patients initiating treatment in the MAA, the figures from baseline to 24 months were:

- +46.8 (69.3) % (n=14) in 6MWT;
- +13.9 (20.2) % (n=14) in FVC;
- +12.7 (20.7) % (n=13) in FEV1;
- -52.6 (18.3) % (n=16) in uKS; and
- +5 (23) % (n=15) in ejection fraction.

Mean (SD) % changes from baseline to last follow-up were for ex-trial patients were:

- +7.1 (33.6) % (n=21) in 6MWT distance;
- +27.2 (34.2) % (n=24) in FVC;

- +23.0 (27.5) % (n=24) in FEV1;
- -56.8 (17.6) % (n=24) in uKS; and
- -2 (11) % (n=19) in ejection fraction.

All patients met criteria to continue treatment. Real-world data from the MAA shows treatment elosulfase alfa in patients with MPS IVA resulted in an overall improvement or stabilisation of clinical outcomes with maintenance of function when treated long-term. Results are significant given the progressive nature of the disorder.

A manuscript is expected to be published in Orphanet in early 2021 based on an earlier data cut-off from May 2019, which included [redacted] patients in the analysis, of which [redacted] were treatment-naïve and [redacted] were previously enrolled in the clinical trials in England. The results presented in this manuscript are consistent with the latest results from [redacted] data-cut that are presented in this dossier.

Correlations between measures

A pairwise correlation was performed to assess the correlation across the clinical measures and PROs. Change from baseline were calculate to ERT-Naïve patients and Ex-Trials across all outcomes of interested listed in (Table 42). Listwise deletion was used to handle with missing data, resulting in 32 patients in the final analysis.

Lung function as measured by FVC is inversed and significantly correlated to 6MWT, indicating patients who deteriorate in 6MWT from baseline also worsen in lung function. As anticipated, FVC and FEV1 were positively significantly correlated.

In the PROs, self-care domain of MPS-HAQ is inversed and significant correlated to FEV1 which could indicate activities of self-care are impacted by lung function. Mobility domain and self-care doming from MPS-HAQ are significant positively correlated as anticipated, whilst EQ-5D is inversed

and significantly correlated to MPS-HAQ in both domains (Mobility and Self-care).

Table 42. Pearson's correlations between clinical measures change from baseline

Variables	6MWT	FVC	FEV1	uKS	EQ-5D	MPS-HAQ (Mobility domain)	MPS-HAQ (Self-care domain)
6MWT	[redacted]						
FVC	[redacted]	[redacted]					
FEV1	[redacted]	[redacted]	[redacted]				
uKS	[redacted]	[redacted]	[redacted]	[redacted]			
EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
MPS-HAQ (Mobility domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MPS-HAQ (Self-care domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Values in bold are different from 0 with a significance level alpha = 0.05

Antibody titres

Immunogenicity data were collected during the MAA, although Safety was not in the scope of the data monitoring under the MAA terms. As observed in Figure 30, it is not possible to correlate the level of antibody titres to treatment adherence.

Figure 30. Antibody Titres overtime in patients On treatment and Off treatment, by age at baseline

[redacted]

Discussion

Overall, the real-world MAA data confirm the long-term effects of elosulfase alfa previously demonstrated in clinical trials (Sections 9.6 and 9.8). In line with international guidelines, elosulfase alfa alongside multidisciplinary care can positively impact clinical and PRO measures. Patients enrolled in the programme showed a rapid decrease and a subsequent stabilisation in the long term in normalised uKS, as well as initial improvements in endurance and pulmonary function and stabilisation in these measures in the long term. In addition, patients' ability to perform ADL and the need for caregiver assistance improved or remained stable in the long run. The finding that almost all patients in the MAA remained on therapy during the study period further confirms clinical stability, since patients were only allowed to continue treatment if they met four out of five MAA clinical and PRO criteria outlined in

Table 9. Although safety data were not collected as part of the MAA, an analysis of MAA patients who also participated in the MARS registry supported the acceptable safety profile of elosulfase alfa.

Favourable results were seen across different study (patients initiating treatment in the MAA, in MOR-002, or in other clinical trials) and age subgroups, confirming the effectiveness of treatment regardless of demographic and baseline characteristics. In patients who started therapy in the MAA, mean changes from pre-treatment baseline in 6MWT distance ([redacted]m) and uKS ([redacted]%) were in accordance with those reported in the clinical trials. In patients from the MOR-004/005 Intent-To-Treat population continuously treated with elosulfase alfa 2.0 mg/kg/week, least square mean changes from baseline after 2 years were +32 m for 6MWT distance and -59.4% for uKS (Hendriksz et al., 2016c). Patients who were previously enrolled in clinical trials and had been on therapy for up to 10 years showed long-term stability of endurance and pulmonary function, as compared with a deterioration in untreated (MOR-001) patients. Trends towards improvement or stabilisation of these outcomes were seen regardless of age at which treatment was started (before or after 18 years of age).

Most of the differences in baseline data between the trial subgroups can be explained by different ages at treatment initiation. Patients previously enrolled in MOR-002 were overall younger than those included in other clinical trials and those initiating treatment in the MAA. Younger patients generally have a higher uKS (which decreases with aging), and a lower weight and pulmonary capacity (which both increase with growth). However, whereas 6MWT distance increases with age in healthy children and adolescents (Lammers et al., 2008, Li et al., 2007), patients in MOR-002 showed greater baseline 6MWT distances than those in the other (older) subgroups, confirming the detrimental impact of disease progression on endurance/mobility.

As all patients in the MAA received elosulfase alfa, outcomes could not be directly compared with a control group of untreated patients to assess the impact of treatment on the disease course. Therefore, 6MWT results were interpreted in the context of the MOR-001 natural history data extrapolation. Overall, untreated patients showed a clear deterioration in 6MWT distance over time, while mean 6MWT results remained above baseline levels for treated patients throughout the study period, regardless of

trial history or age at treatment initiation. In addition, all trial subgroups showed better pulmonary function outcomes over 3 years than the MOR-001 population. MPS-HAQ results at 2 years in the MAA were also more favourable than those reported for the MOR-001 population, which showed a deterioration in Mobility and Self-care over the same time period (Hendriksz et al., 2018b). Overall, these results suggest that ERT can slow down the gradual regression in endurance associated with MPS IVA.

The MAA is the first study in MPS IVA patients showing a correlation between pulmonary function measures and 6MWT results. This is in line with findings in other diseases associated with impaired lung function (Wibmer et al., 2014). These findings suggest that pulmonary function can explain at least part of the variance in 6MWT outcomes in MPS IVA patients. However, changes in 6MWT distance are not influenced by changes in pulmonary function alone, but also by other factors such as joint mobility, pain, cardiac function, or a combination of these factors that differ from patient to patient. Surgical procedures, which were allowed during the study, could also have (temporarily) influenced 6MWT results and wheelchair status in some of the patients.

A limitation of the analysis is that pre-treatment baseline data were not available for all patients, due to young age at treatment initiation or endpoint not being measured at baseline for ex-trial patients. In these cases, the first measure during the MAA period had to be used as baseline. However, for most endpoints, only a minority of the total study population had no pre-treatment baseline. Moreover, the use of baseline measures collected after treatment initiation may have resulted in an underestimation, rather than an overestimation, of treatment effects. Finally, some of the follow-up data during the programme were missing due to patients being unable to complete the test at the time of the measurement (due to age, surgery, illness), or a delay in processing for lab measures. This led to low patient numbers in some of the analyses.

It should be emphasised that none of the measures evaluated in the MAA can be considered an accurate reflection of the benefits of treatment on its own. Due to the wide phenotypic heterogeneity of MPS IVA patients, it is important to look at different measures in concert, supporting a holistic approach for monitoring these patients.

Final remarks about the results from the MAA

Overall, the real-world, long-term results of the MAA are meaningful for patients with MPS IVA, who typically experience early morbidity and mortality without treatment. Initial improvements observed in the MAA are aligned with those observed in the clinical trials (MOR-004/005) and long-term outcomes show a broad stabilisation in patients who remain treated in the MAA. The MAA maintenance criteria successfully removed patients who had poorer outcomes. The presented data therefore provides further evidence that long-term treatment with elosulfase alfa has a positive impact on patients' quality of life and ability to perform ADL and stabilises or improves pulmonary function and endurance, while lessening patients' need for caregiver assistance. The results observed during the period of the MAA and described above address the uncertainties on the long-term outcomes of elosulfase alfa pointed by The Committee in the first appraisal in 2015 (NICE, 2015b), confirming the clinical effectiveness of elosulfase alfa treatment.

9.6.1.2.2 MARS (Morquio A Registry Study): Long-term outcomes from patients treated worldwide

Recent results presented during the WORLD*Symposium*™ congress on February 2020

The WORLD*Symposium*™ congress was held between from February 10th to 13, 2020. This is an annual research conference dedicated to lysosomal diseases, which had its first edition on 2002 and now in 2020 received over 1.900 participants from more than 50 countries around the globe.[b]

Two posters were presented during the congress outlining the 5-year real-world results from MARS, as follow:

- **1st Poster: Long-term clinical outcomes of patients treated with elosulfase alfa: Five-year real-world results from the Morquio A Registry Study (MARS)**

[b] https://worldsymposia.org/about-worldsymposia-lysosomal-cell-biology/

The evaluation of clinical data of ERT-treated patients included changes from pre-treatment baseline to last follow-up (data cut-off February 13, 2019) for 6-minute walk test (6MWT) distance, pulmonary function (forced vital capacity [FVC] and forced expiratory volume in 1 second [FEV1]), and uKS. Data were evaluated separately for patients who initiated ERT in clinical trials and independent of clinical trials, and for different age categories (<18 years and ≥18 years of age at treatment initiation) Statistical tests were paired t-tests for change of clinical outcomes from pre-treatment baseline

Patient Characteristics

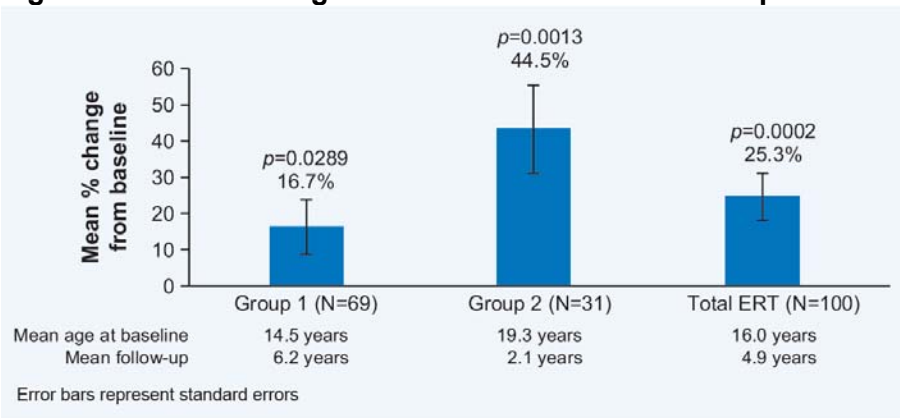
As of February 13, 2019, 325 patients enrolled in MARS (mean age: 17.7 years), including 262 ERT-treated patients. From the 262 ERT-Treated patients, 119 initiated ERT in clinical trials (Group 1, mean age at treatment initiation 13.7 [range 0.8–57.5] years; mean treatment duration: 6.39 years) and 143 patients initiated ERT independent of clinical trials (Group 2, mean age at treatment initiation 14.9 [range 0.1–62.0] years; mean treatment duration: 2.77 years).

Results

6-Minute walk test

In patients with baseline and at least one follow-up assessment reported, mean (SD) 6MWT distance at pre-treatment baseline was 224.7 (88.35) m for Group 1 (N=70) and 277.7 (162.07) m for Group 2 (N=31). In both groups, patients showed statistically significant increases in 6MWT distance from baseline to last follow-up (Figure 31)

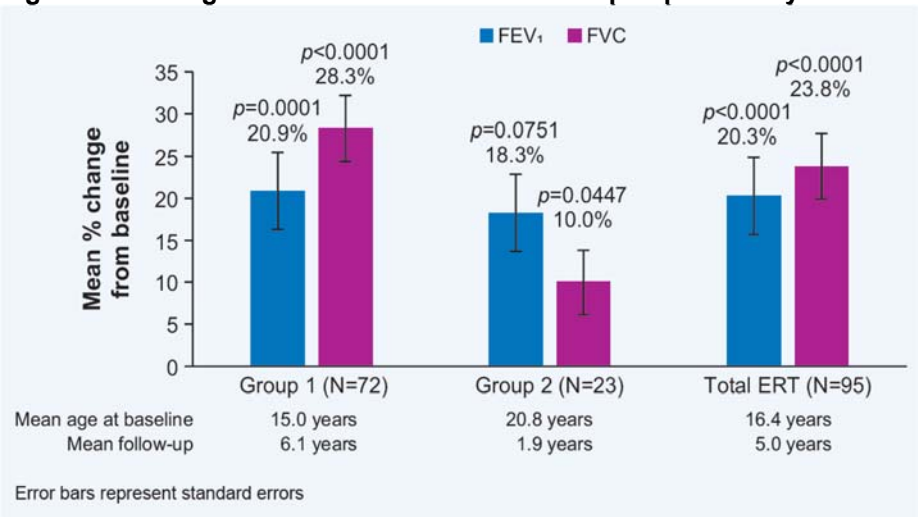
Figure 31. 6MWT change from baseline to last follow-up



Pulmonary function

At pre-treatment baseline, patients with baseline and at least one follow-up assessment in Group 1 had a mean (SD) FEV1 of 0.9 (0.64) L and a mean FVC of 1.1 (0.80) L (N=72); in Group 2, mean values were 1.3 (1.09) L and 1.6 (1.46) L, respectively (N=23). In both groups, patients showed significant or a trend to significant increases in FEV1 and FVC from baseline to last follow-up (Figure 32).

Figure 32. Change from baseline to last follow-up in pulmonary function measures



1st Poster Conclusions

Morquio A patients treated with elosulfase alfa up to 6 years in MARS show improved clinical outcomes long-term. The initial improvements in the 6MWT and pulmonary function in naïve patients at enrollment (Group 2) are similar to what was observed in clinical trials. Long-term data (Group 1) show sustained improvement in these measures.

These real-world results confirm the long-term efficacy outcomes of clinical trials, showing sustained reductions in uKS and suggesting a stabilization of endurance and pulmonary function outcomes with treatment, which is clinically meaningful given the progressive and debilitating nature of MPS IVA.

The results of the analyses comparing patients <18 vs. ≥18 years of age at treatment initiation require further investigation. Differences in 6MWT results may be due to phenotypical differences (e.g. more classical phenotypes in the younger cohort);

increases in the 6MWT and FEV1/FVC in younger patients can be (partly) due to growth.

Limitations of the analysis include varying treatment durations and differing standards of care leading to variable follow-up assessment frequency.

Real-world 6MWT and pulmonary function test data registered in MARS were limited, even for many of the patients who initiated treatment in the clinical trials. This stresses the importance of a more universal implementation of these tests into standard of care, both for baseline evaluation and routine monitoring.

- **2nd poster: Long-term treatment with elosulfase alfa has an acceptable safety profile for patients with Morquio A: Real-world results from the Morquio A Registry Study (MARS)**

MARS was initiated in 2014 and will continue for up to 10 years. Eligible patients have a confirmed diagnosis of Morquio A by either an enzymatic test or by a molecular test Medical history, and clinical and safety assessments from Morquio A patients are collected in accordance with local standards of care

The safety evaluation (data cut-off February 13, 2019) of ERT-treated patients included:

- Adverse events (AEs) and serious adverse events (SAEs) based on MedDRA version 20.0, regardless of
- causality, occurring within 24 hours of elosulfase alfa infusion
- Infusion interruptions/discontinuations and permanent treatment discontinuations
- Immunogenicity results

Patient Characteristics

As of the data cut-off, 325 patients enrolled in MARS (mean age: 17.7 years), including 262 ERT-treated patients (mean treatment duration: 4.4 years):

- 119 patients initiated ERT in clinical trials (mean treatment duration: 6.37 years)
- 143 patients initiated ERT independent of clinical trials (mean treatment duration: 2.77 years)

Adverse Events

74 ERT-treated patients (28.2%) experienced at least one AE (Table 42). Most common AEs (≥5% incidence) were characterized as musculoskeletal-related, infections/infestations, administration site-related, and nervous system disorders.

61% of all AEs were considered mild/moderate (Grade 1 or 2) in severity and 49 ERT-treated patients (18.7%) experienced at least one SAE. Most common SAEs were cervical cord compression (N=5, 1.9%), knee deformity (N=5, 1.9%), and developmental hip dysplasia (N=3, 1.1%), which are related to disease progression; incidence of all other SAEs was <1%.

Table 42. Summary of AEs in patients receiving elosulfase alfa (N=262)

	Incidence N (%)	Events[a]
Subjects with		
≥1 reported AE	74 (28.2%)	154
≥1 reported SAE	49 (18.7%)	69
≥1 study drug-related AE	23 (8.8%)	68
≥1 AE leading to permanent treatment discontinuation	0	0
Death		
Unrelated to ERT	5 (0.02%)	
Related to ERT	0	

Mapping was based on MedDRA version 20.0. Subjects who experience more than 1 AE within a given MedDRA system organ class or preferred term were counted once within that system organ class or preferred term.
[a]Multiple events were counted if a subject had the same AE with different onset dates or times. AEs with change of severity may be counted multiple times

23 ERT-treated patients (8.8%) experienced at least one drug-related AE. Most common were urticaria (2.3%), hypersensitivity (1.9%), nausea (1.5%), pyrexia (1.5%), and headache (1.1%); incidence of all other drug-related AE was <1%

Four SAEs in three patients were considered drug-related:

- Two Grade 2 allergic/anaphylactic reactions requiring drug interruption
- Two infusion-related reactions (one Grade 3, one Grade 2 [required drug interruption]) in the same patient

- All drug-related SAEs were resolved

Infusion interruption due to an AE was reported in two patients; one subsequently continued with the infusion following the interruption while the other did not. No patient permanently discontinued ERT due to an AE and 5 ERT-treated patients died.

Immunogenicity

All patients (N=262) developed anti-drug total antibodies (TAb) after 24 weeks of treatment, and most patients (≥ 89%) remained TAb positive throughout. Nearly all patients tested positive for neutralizing antibodies at least once (74.1% at the 5-year analysis visit)

2nd Poster conclusion

Overall, real-world results from MARS revealed no new safety concerns. These results corroborate and confirm the acceptable long-term safety profile of elosulfase alfa as observed in clinical trials.

Overall, the registry immunogenicity data, though sparse, appears to be consistent with data previously reported for the clinical trials. No correlation between antibody results and the incidence or severity of AEs was seen in the clinical trials.

Other published evidence:

Mitchell et al. 2020 presented long-term clinical outcomes of patients treated with elosulfase alfa: Five-year real-world results from the Morquio A Registry Study (MARS).

As of February 13, 2019, 325 patients enrolled in MARS (mean age: 17.7 years); 262 are ERT-treated (n = 119 ERT initiated in clinical trials [Group 1, mean treatment duration: 6.37 years], n = 143 ERT initiated independent of clinical trials [Group 2, mean treatment duration: 2.77 years]).

Prior to treatment (baseline for all outcomes), Groups 1 (n = 78) and 2 (n = 29) had 6MWT values (meters [m], mean [standard error,SE]) of 245.5 (10.93) and 292.9 (25.34) m, respectively.

At last recorded assessment compared to baseline, mean(SE) percentage change in 6MWT was 16.7(7.46)% in Group 1 (n = 69, p =.0289; baseline to last assessment mean treatment duration: 5.77 years) and 45.8(13.36)% in Group 2 (n = 29, p =.0019; 1.9 years treatment duration), respectively. At baseline, Group 1 (n = 85) had FEV1 and FVC values (liters [L]) of 1.0(0.08) and 1.1(0.10) L and Group 2 (n = 31) had values of 1.2(0.18) and 1.4(0.23) L. Group 1 (n = 72; 5.66 years treatment duration) had a percentage change in FEV1 of 20.9(5.19)% (p =.0001) and FVC of 28.3(4.78)% (p <.0001), and Group 2 (n = 23; 1.41 years treatment duration) had a percentage change in FEV1 of 18.3(9.79)% (p =.0751) and FVC of 10.0(4.67)% (p =.0447). At baseline, Groups 1 (n = 98) and 2 (n = 25) had normalized uKS of 26.8(1.76) and 25.3(6.10) µg/mg creatinine, respectively. Percentage change in uKS was −49.4(4.19) % in Group 1 (n = 69, p <.0001; 5.60 years treatment duration) and − 44.3(4.53) % in Group 2 (n = 20, p <.0001, 0.95 years treatment duration).

Patients treated with ERT up to ~6 years in MARS show trends toward improved clinical outcomes long-term.

Final remarks about the results from MARS

The data collected and analysed in the real-world setting demonstrate the positive outcomes of elosulfalse alfa treatment in a broader population and confirms the durability of the benefit in the long-term. There were no new safety concerns identified, and most frequent SAEs were disease related.

Considering this new real-world evidence, uncertainties raised in relation to the previous appraisal may be significantly reduced.

9.6.1.2.3 Real-world studies conducted in other countries

Real-world data in seven paediatric patients aged 7-17 years with severe clinical manifestations of MPS IVA were reported from Spain by Pintos-Morell et al. 2018. Follow-up was from baseline to 8 months with elosulfase alfa treatment. 6MWT improved in all patients except one (range was 0-325m at BL and 12-300m at follow-up. In two patients who used wheelchairs, 6MWT improved from 0m at BL to 24m, and

from 20m to 32m. 3MSCT improved in 4 patients, was unchanged in 2 patients and unavailable in 1 pt. Five patients improved their FVC (range of 4-19% increases from BL), 1 was unchanged and 1 had reduced FVC after 8 months. EQ-5D-5L was measured but only the EQ-VAS score reported. There were no SAEs and ESA treatment was not interrupted (Pintos-Morell et al., 2018).

Neurocognitive data were reported in Rigoldi et al., 2014. Mean (SD) IQ in 13 MPS IVA patients in ITA was 91.6 (21), range 61 to 125. Two 11-year-old patients had mild mental retardation (total IQ 61 and 66). Three patients had borderline mental retardation (total IQ 78, 73, 75). Eight patients had normal total IQ. Of the 5 patients with total IQ lower than 80, four had chronic respiratory insufficiency of which 1 had nocturnal apnoea with adenotonsillar hypertrophy and laryngomalacia, and 3 were on non-invasive ventilation. The lowest IQs may be explained by hypoxia due to the respiratory insufficiency. Verbal IQ was higher than performance IQ (mean (SD), range 94.8 (21.2), 65-121 vs 88.7 (19.6), 59-124, respectively), which may be due to musculoskeletal and spinal disease (Rigoldi et al., 2014).

Lampe et al. 2015 (Lampe et al., 2015) showed statistically significant correlation between EQ-5D-5L and endurance outcomes (6MWT r=0.713, p=0.0019; 3MSCT r=0.693, p=0.0060) or pulmonary function (FVC r=0.521, p=0.0155; MVV r=0.534, p=0.0126) in German patients with MPS IVA, suggesting that improvements in these clinical outcomes could be robust surrogates for better HRQoL. Mean (SD) EQ-5D-5L in 21 patients was 0.552 (0.342), 0.422 (0.363) in 13 adults and 0.763 (0.160) in 8 children. Correlations between these parameters in children were poor and non-significant for all outcomes. The correlations were strongest in adults, with correlations between EQ-5D-5L and endurance outcomes (6MWT r=0.884, p=0.0016, n=9; 3MSCT r=0.852, p=0.0149, n=7) or pulmonary function outcomes (FVC r=0.815, p=0.0007, n=13; MVV r=0.825, p=0.0005, n=13) being statistically significant. Regression analysis showed that 6MWT was more closely correlated with EQ-5D-5L: an increased 6MWT of 100m was associated with an increase of 0.2 in EQ-5D-5L.

Hendriksz et al. 2014 (Hendriksz et al., 2014c)described the burden of 56 caregivers to MPS IVA patients in an international PRO survey, from Brazil, Columbia, Germany, Spain and Turkey. Mean age of caregivers (N=54) was 42.6 yrs and the vast majority were mothers (82.1%, N=56). Seventy-three percent cared for 1 pt with MPS IVA, and

27% 2 patients. They recorded the amount of time spent on caregiving, the percentage of daily activities of the patient requiring caregiver assistance (using the MPS HAQ) and the effect of patient age and wheelchair use on these aspects. They identified that improving the patient's mobility may reduce the amount of caregiver support required and caregiver burden. The domain-level MPS HAQ data were NR but the %s of patients requiring assistance with specific ADL, as measured by MPS HAQ, were reported (in Fig. 3a (adults) and 3b (children) of the FP). Wheelchair use in adult patients had an impact on the % of activities that patients required complete assistance with from the caregiver: 68% of activities if the patient always used a wheelchair, 12% if the patient only used a wheelchair when needed, and 0% in patients not using wheelchairs. The % of activities performed independently in these three wheelchair use groups of patients was 4%, 29% and 70%, respectively. The differences seen in % of activities requiring caregiver assistance for adult patients, was not so apparent for caregivers to child patients.

Nagao et al. 2018 (Nagao et al., 2018)reported a strong association between reduced height (an indication of skeletal severity) and hearing loss (pure tone threshold average right ear r=-0.59 ($p<0.005$) and left ear r=-0.71 ($p=0.01$); distortion products otoacoustic emissions (DPOAE, a measure of inner ear function) right ear r=-0.84 ($p<0.0001$) and left ear r=-0.87 ($p<0.0001$)) in 13 MPS IVA patients. There was also strong association between height and outer hair cell function of the inner ear (measured using otoacoustic emissions). The authors suggested that patients with more severe skeletal dysplasia may be at higher risk of more severe hearing loss and that patients should have yearly neurophysiological hearing tests (auditory brainstem responses and otoacoustic emissions test) as well as audiometric testing from an early age.

Finnigan et al. 2018 (Finnigan et al., 2018) described their experience with home infusion with elosulfase alsa in 14 MPS IVA children (aged 4-16 years) and made recommendations for successful home treatment. Elosulfase alfa treatment at home was considered more convenient for the patient and their family, in the context of a weekly lifelong infusion (each of average duration 4-5 hours). Travel time, impact on schooling and cost implications have been discussed in the Economic/Cost SR section. The recommendations included: first fully establishing treatment with

Elosulfase alfa with either no infusion-related reactions (IRRs) or IRRs that are appropriately managed in the hospital setting (at least 12 weeks) before transitioning to the home setting; established i.v. access; individual assessment by the lysosomal storage disease (LSD) team for homecare treatment; a member of the healthcare at home team should meet the patient at the treatment setting prior to the patient transferring from the hospital to check venous access and pre-medication regime, and they should also visit the home setting to ensure it is appropriate for preparing and administering ESA; the family doctor should be informed that the patient is transferring for home infusions and whether there are any IRRs or a totally implanted venous access device (TIVAD); nurses must be trained in ERT administering and caring for children with LSDs, and annually in resuscitation and anaphylaxis; each nurse will have individualized kit in the event of IRRs; homecare team sends a weekly report to the treatment centre; regular contact with the hospital should be maintained via a direct phone line to the LSD treatment centre, dedicated 24-hr nurse on-call service and a dedicated Monday-Friday customer service team (8a.m.-6p.m.).

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

In the MOR-005 trial, the ITT population is confounded by surgery and the subsequent period of recovery, which impact directly the primary endpoint (6MWT) of the trial. The other populations are confounded by the times of transition to the indicated dose and as such not representing long term use of elosulfase alfa.

The modified per protocol (MPP) population is proposed as patients who retained acceptable compliance of >80% and have not undergone surgery, which represent the relevant population to evaluate the long-term effect of the license dose (QW-QW population).

9.7 **Adverse events**

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search were extracted and reported in the section 9.7.2.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

Adverse Events (AEs) and at least possibly treatment-related AEs are presented in Table 43. Adverse Drug Reactions (ADRs) are presented in Table 44. Serious Adverse Events (SAEs) are presented in Table 45. SAEs (serious adverse events) at least possibly related to treatment are presented in Table 46 and mortality is presented in Table 47.

Table 43. Adverse events

Study ID	Author, Year, Endnote ID	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
MOR-002	Hendriksz, Santra et al.,2018a	ESA 0.1 mg/kg qw	12	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	18	90.0	Across all ESA: most AEs were mild-moderate in severity. Incidence did not increase with increasing dose or exposure.
		ESA 1.0 mg/kg qw	13 - 24	wks	All safety pts		NR	18	18	100.0	
		ESA 2.0 mg/kg qw	25 - 36	wks	All safety pts		NR	18	17	94.4	
		Continuation period ESA 1.0 mg/kg qw	36 - 48	wks	All safety pts		NR	18	17	94.4	
		Overall MOR-002	72 - 84	wks	All safety pts		NR	20	20	100.0	
MOR-100	Hendriksz, Santra et al., 2018a	ESA 2.0 mg/kg qw	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	17	17	100.0	
MOR-002/MOR-100	Hendriksz, Santra et al., 2018a	Combined MOR-002/MOR-100	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	20	100.0	
MOR-004	Hendriksz, Burton et al., 2014b	PLA	24	wks	All safety pts	MedDRA v15.0	NR, mean dose compliance across all tx arms ranged from 96.8% to 99.2%	59	57	96.6	
		ESA 2.0 mg/kg qow	24	wks	All safety pts			59	59	100.0	
		ESA 2.0 mg/kg qw	24	wks	All safety pts			58	56	96.6	
MOR-005	Hendriksz, Parini et al., 2016c	PLA - ESA 2.0 mg/kg qow	120	wks	All safety pts (reported as ITT but also	MedDRA v16.1	NR	29	29	100.0	Most common AEs were mild to

Study ID	Author, Year, Endnote ID	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
		PLA - ESA 2.0 mg/kg qw	120	wks	as all patients that received any dose of study drug and had any post-treatment safety information)	MedDRA v16.1	NR	29	29	100.0	moderate IARs (e.g. vomiting, pyrexia, headache) and managed with tx of symptoms and/or modifying the infusion rate.
		ESA 2.0 mg/kg qow - ESA 2.0 mg/kg qow	120	wks		MedDRA v16.1	NR	59	59	100.0	
		ESA 2.0 mg/kg qw - ESA 2.0 mg/kg qw	120	wks		MedDRA v16.1	NR	56	56	100.0	
MOR-006	Harmatz et al., 2017	ESA 2.0 mg/kg qw	96	wks	All safety pts (mITT population - all pts randomized to study tx and received at least one dose of study drug)	MedDRA v16.1, CTCAE	Mean [SE] 62.1 [8.01], range 5-96 wks	15+	15	100	Most AEs were mild-moderate in severity (CTCAE grade 1 or 2).
MOR-007	Jones et al, 2015; NCT 2017	ESA 2.0 mg/kg qw	52	wks	All safety pts (all enrolled pts)	MedDRA v15.0*, CTCAE	All pts had at least 88% dosing compliance. Mean weekly dose received was 1.9 (SD (assumed	15	15	100	Most AEs mild-moderate in severity.

Study ID	Author, Year, Endnote ID	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
							SD, NR) 0.1) mg/kg/pt				

Abbreviations: AE, adverse event; CTCAE, Common Toxicity Criteria for Adverse Events; ESA, elosulfase alfa; IAR, infusion-associated reaction; mITT, modified intention-to-treat; PLA, placebo; pts, patients; qow, every other week; qw, weekly; SD, standard deviation; SE, standard error; tx, treatment; wks, weeks
+ 16 pts enrolled in MOR-006 but only 15 received study drug, so safety population N=15.
* In Jones et al., 2015, AEs coded by MedDRA v15.0. In NCT record (NCT 2017) indicated that AEs coded by MedDRA v16.1.

Table 44. Adverse drug reactions

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
MOR-002	Hendriksz, Santra et al., 2018a	ESA 0.1 mg/kg qw	12	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	12	60.0	Across all ESA: Most frequent ADRs were pyrexia (45%), headache (40%) and increased total IgE (30%).
		ESA 1.0 mg/kg qw	13 - 24	wks			NR	18	10	55.6	
		ESA 2.0 mg/kg qw	25 - 36	wks			NR	18	7	38.9	
		Continuation period ESA 1.0 mg/kg qw	36 - 48	wks			NR	18	8	44.4	
		Overall MOR-002	72 - 84	wks			NR	20	14	70.0	
MOR-100	Hendriksz, Santra et al., 2018a	ESA 2.0 mg/kg qw	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	17	16	94.1	
MOR-002/MOR-100	zCombined MOR-	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	19	95.0		

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
	002/MOR-100										
MOR-004	Hendriksz, Burton et al.,2014b	PLA	24	wks	All safety pts	MedDRA v15.0	NR, mean dose compliance across all tx arms ranged from 96.8% to 99.2%	59	36	61.0	
		ESA 2.0 mg/kg qow	24	wks				59	42	71.2	
		ESA 2.0 mg/kg qw	24	wks				58	42	72.4	
MOR-005	Hendriksz, Parini et al., 2016c	PLA - ESA 2.0 mg/kg qow	120	wks	All safety pts +	MedDRA v16.1	NR	29	23	79.3	
		PLA - ESA 2.0 mg/kg qw	120	wks			NR	29	20	69.0	
		ESA 2.0 mg/kg qow - ESA 2.0 mg/kg qow	120	wks			NR	59	40	67.8	
		ESA 2.0 mg/kg qw - ESA 2.0 mg/kg qw	120	wks			NR	56	43	76.8	
MOR-006	Harmatz et al., 2017	ESA 2.0 mg/kg qw	96	wks	All safety pts (mITT population) #	MedDRA v16.1, CTCAE	Mean [SE] 62.1 [8.01], range 5-96 wks	15 *	13	86.7	Most common ADRs headache (40%), nausea, pyrexia, vomiting (20% each).
MOR-007	Jones et al., 2015; NCT 2017	ESA 2.0 mg/kg qw	52	wks	All safety pts (all	MedDRA v15.0 §, CTCAE	All pts had at least 88% dosing	15	11	73.3	Most common ADRs were pyrexia (40%)

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
					enrolled pts)		compliance ¶				and vomiting (33.3%).

+ Reported as ITT but also as all patients that received any dose of study drug and had any post-treatment safety information
* 16 pts enrolled in MOR-006 but only 15 received study drug, so safety population N=15.
# mITT defined as all pts randomized to study tx and received at least one dose of study drug
§ In Jones 2015 AEs coded by MedDRA v15.0. In NCT record indicated that AEs coded by MedDRA v16.1.
Mean weekly dose received was 1.9 (SD (assumed SD, NR) 0.1) mg/kg/pt

Table 45. Serious adverse events

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
MOR-002	Hendriksz, Santra et al., 2018a	ESA 0.1 mg/kg qw	12	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	6.0	30.0	Across all ESA: Majority of SAEs were complications of MPS IVA or cannulation difficulties.
		ESA 1.0 mg/kg qw	13 - 24	wks			NR	18	2.0	11.1	
		ESA 2.0 mg/kg qw	25 - 36	wks			NR	18	8.0	44.4	
		Continuation period ESA 1.0 mg/kg qw	36 - 48	wks			NR	18	6.0	33.3	
		Overall MOR-002	72 - 84	wks			NR	20	14.0	70.0	
MOR-100	Hendriksz, Santra et al., 2018a	ESA 2.0 mg/kg qw	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	17	15.0	88.2	

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
MOR-002/MOR-100	Hendriksz, Santra et al., 2018a	Combined MOR-002/MOR-100	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	19.0	95.0	
MOR-004	Hendriksz, Burton et al., 2014b	PLA	24	wks	All safety pts	MedDRA v15.0	NR, mean dose compliance across all tx arms ranged from 96.8% to 99.2%	59	2	3.4	
		ESA 2.0 mg/kg qow	24	wks				59	4	6.8	
		ESA 2.0 mg/kg qw	24	wks				58	9	15.5	
MOR-005	Hendriksz, Parini et al., 2016c	PLA - ESA 2.0 mg/kg qow	120	wks	All safety pts (reported as ITT+)	MedDRA v16.1	NR	29	16 in FP 17 in NCT record	55.2 (58.62% in reg record)	Most SAEs related to planned surgery
		PLA - ESA 2.0 mg/kg qw	120	wks			NR	29	14 (15 in reg record)	48.3 (51.72% in reg record)	
		ESA 2.0 mg/kg qow - ESA 2.0 mg/kg qow	120	wks			NR	59	24 (26 in reg record)	40.7 (44.07% in reg record)	
		ESA 2.0 mg/kg qw - ESA 2.0 mg/kg qw	120	wks			NR	56	23 (31 in reg record)	41.1 (55.36% in reg record)	
MOR-006	Harmatz et al., 2017	ESA 2.0 mg/kg qw	96	wks	All safety pts (mITT population) #	MedDRA v16.1, CTCAE	Mean [SE] 62.1 [8.01], range 5-96 wks	15 *	7	46.7	SAE data on registry record NCT01697319

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
MOR-007	Jones et al., 2015; NCT 2017	ESA 2.0 mg/kg qw	52	wks	All safety pts (all enrolled pts)	MedDRA v15.0 (see notes), CTCAE	All pts had at least 88% dosing compliance §	15	4	26.7	¶

+ But also reported as all patients that received any dose of study drug and had any post-treatment safety information
* 16 pts enrolled in MOR-006 but only 15 received study drug, so safety population N=15.
# mITT defined as all pts randomized to study tx and received at least one dose of study drug
§ Mean weekly dose received was 1.9 (SD (assumed SD, NR) 0.1) mg/kg/pt
The frequency of SAEs reported in the NCT registry record last updated August 10, 2017 was reported as 8/15 (53.33%), which is discrepant from that reported in Jones 2015.
In Jones 2015 AEs coded by MedDRA v15.0. In NCT record indicated that AEs coded by MedDRA v16.1.

Table 46. Serious adverse possibly related to the treatment

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
MOR-002	Hendriksz, Santra et al., 2018a	ESA 0.1 mg/kg qw	12	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	2.0	10.0	Most common tx-related SAEs were injection site reactions (10%) and pyrexia (10%). Others resulted from hypersensitivity reactions.
		ESA 1.0 mg/kg qw	13 - 24	wks			NR	18	1.0	5.6	
		ESA 2.0 mg/kg qw	25 - 36	wks			NR	18	2.0	11.1	
		Continuation period ESA 1.0 mg/kg qw	36 - 48	wks			NR	18	1.0	5.6	
		Overall MOR-002	72 - 84	wks			NR	20	4.0	20.0	
MOR-100	Hendriksz, Santra et al., 2018a	ESA 2.0 mg/kg qw	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	17	6.0	35.3	
MOR-002/MOR-100	Hendriksz, Santra et al, 2018a	Combined MOR-002/MOR-100	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	9.0	45.0	
MOR-004	Hendriksz, Burton et al., 2014b	PLA	24	wks	All safety pts	MedDRA v15.0	NR, mean dose compliance across all tx arms ranged from 96.8% to 99.2%	59	0	0.0	
		ESA 2.0 mg/kg qow	24	wks				59	1	*1.7*	1 anaphylactic reaction that resolved same day with tx and reduced infusion rate
		ESA 2.0 mg/kg qw	24	wks				58	2	*3.4*	1 hypersensitivity reaction, resolved in 24 hrs with tx and infusion discontinuation, and 1 severe vomiting case

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
											that resolved same day without medication.
MOR-005	Hendriksz, Parini et al., 2016c	PLA - ESA 2.0 mg/kg qow	120	wks	All safety pts +	MedDRA v16.1	NR	29	2	6.9	2 tx-related SAEs occurred in separate pts: anaphylaxis (grade 4) and hematuria (grade 2).
		PLA - ESA 2.0 mg/kg qw	120	wks			NR	29	0	0.0	
		ESA 2.0 mg/kg qow - ESA 2.0 mg/kg qow	120	wks			NR	59	0	0.0	
		ESA 2.0 mg/kg qw - ESA 2.0 mg/kg qw	120	wks			NR	56	0	0.0	
MOR-006	Harmatz et al., 2017	ESA 2.0 mg/kg qw	96	wks	All safety pts (mITT population #)	MedDRA v16.1, CTCAE	Mean [SE] 62.1 [8.01], range 5-96 wks	15 *	2	13.3	
MOR-007	Jones et al., 2015; NCT, 2017)	ESA 2.0 mg/kg qw	52	wks	All safety pts (all enrolled pts)	MedDRA v15.0 §, CTCAE	All pts had at least 88% dosing compliance ¶	15	1	6.7	

+ Reported as ITT but also as all patients that received any dose of study drug and had any post-treatment safety information
* 16 pts enrolled in MOR-006 but only 15 received study drug, so safety population N=15.
# mITT defined as all pts randomized to study tx and received at least one dose of study drug
§ In Jones 2015 AEs coded by MedDRA v15.0. In NCT record indicated that AEs coded by MedDRA v16.1.
¶ Mean weekly dose received was 1.9 (SD (assumed SD, NR) 0.1) mg/kg/pt

Table 47. Mortality

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
MOR-002	Hendriksz, Santra et al., 2018a	ESA 0.1 mg/kg qw	12	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	0	0.0	
		ESA 1.0 mg/kg qw	13 - 24	wks			NR	18	0	0.0	
		ESA 2.0 mg/kg qw	25 - 36	wks			NR	18	0	0.0	
		Continuation period ESA 1.0 mg/kg qw	36 - 48	wks			NR	18	0	0.0	
		Overall MOR-002	72 - 84	wks			NR	20	0	0.0	
MOR-100	Hendriksz, Santra et al., 2018a	ESA 2.0 mg/kg qw	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	17	0	0.0	
MOR-002/MOR-100	Hendriksz, Santra et al., 2018a	Combined MOR-002/MOR-100	240	wks	All safety pts	MedDRA v16.1 / CTCAE	NR	20	0	0.0	
MOR-004	Hendriksz, Burton et al., 2014b	PLA	24	wks	All safety pts	MedDRA v15.0	NR, mean dose compliance across all tx arms ranged from 96.8% to 99.2%	59	0	0.0	
		ESA 2.0 mg/kg qow	24	wks				59	0	0.0	
		ESA 2.0 mg/kg qw	24	wks				58	0	0.0	
MOR-005	Hendriksz, Parini et al., 2016c	PLA - ESA 2.0 mg/kg qow	120	wks	All safety pts +		NR	29	0	*0.0 0*	No new or unexpected safety signals detected

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
		PLA - ESA 2.0 mg/kg qw	120	wks			NR	29	0	*0.0 0*	
		ESA 2.0 mg/kg qow - ESA 2.0 mg/kg qow	120	wks			NR	59	1	*1.6 9*	The death occurred (considered unrelated) as result of postoperative pulmonary complications secondary to spinal cord compression, laminectomy and spinal fusion.
		ESA 2.0 mg/kg qw - ESA 2.0 mg/kg qw	120	wks			NR	56	0	*0.0 0*	
MOR-006	Harmatz et al., 2017	ESA 2.0 mg/kg qw	96	wks	All safety pts (mITT population*)	MedDRA v16.1, CTCAE	Mean [SE] 62.1 [8.01], range 5-96 wks	15 #	0	0.0	
MOR-007	Jones et al, 2015; NCT, 2017	ESA 2.0 mg/kg qw	52	wks	All safety pts (all enrolled pts)	MedDRA v15.0 §, CTCAE	All pts had at least 88% dosing compliance ¶	15	0	0.0	
NR	Harmatz et al., 2013a AB	ESA 2.0 mg/kg qw	1 - 12	wks	Subgroup	NR	Mean (assumed SD) 75.3 (17.49) wks Mean (assumed SD) weekly dose 1.99	52	0	0.0	
		ESA 2.0 mg/kg qw	>48	wks	Subgroup	NR		52	0	0.0	

Study ID	Author, Year,	Study arm	Time-point [no.]	Time-point [unit]	All safety pts or subgroup description	Criteria to measure AEs/ Toxicities	Median duration of tx, wks	Safety population or subgroup N	n	%	Notes
							(0.039) mg/kg				

+ Reported as ITT but also as all patients that received any dose of study drug and had any post-treatment safety information
* mITT defined as all pts randomized to study tx and received at least one dose of study drug
# 16 pts enrolled in MOR-006 but only 15 received study drug, so safety population N=15.
§ In Jones 2015 AEs coded by MedDRA v15.0. In NCT record indicated that AEs coded by MedDRA v16.1.
¶ Mean weekly dose received was 1.9 (SD (assumed SD, NR) 0.1) mg/kg/pt

Real-world, long-term safety:

MAA

No patient in the MAA stopped treatment due to adverse reactions and antibody titres were in line with previously published reports. An analysis of UK patients who consented to participation in MARS shows that less than 40% of patients experienced an adverse event in 2016-2017, all of which were Grade 3 or below and all were resolved. Note that this data-cut includes all patients who consented in the UK, not just those patients who were in the MAA. Additionally, six patients included in the MAA did not consent for their information to be included in the MARS registry and therefore are not included in this analysis. For the latest published safety information on the global population, the label should be consulted (https://www.ema.europa.eu/en/medicines/human/EPAR/vimizim).

MARS

Poster: Long-term treatment with elosulfase alfa has an acceptable safety profile for patients with Morquio A: Real-world results from the Morquio A Registry Study (MARS)

The safety evaluation (data cut-off February 13, 2019) of ERT-treated patients included:

- Adverse events (AEs) and serious adverse events (SAEs) based on MedDRA version 20.0, regardless of
- causality, occurring within 24 hours of elosulfase alfa infusion
- Infusion interruptions/discontinuations and permanent treatment discontinuations
- Immunogenicity results

Patient Characteristics

As of the data cut-off, 325 patients enrolled in MARS (mean age: 17.7 years), including 262 ERT-treated patients (mean treatment duration: 4.4 years):

- 119 patients initiated ERT in clinical trials (mean treatment duration: 6.37 years)
- 143 patients initiated ERT independent of clinical trials (mean treatment duration: 2.77 years)

Adverse Events

74 ERT-treated patients (28.2%) experienced at least one AE (Table 48). Most common AEs (≥5% incidence) were characterized as musculoskeletal-related, infections/infestations, administration site-related, and nervous system disorders.

61% of all AEs were considered mild/moderate (Grade 1 or 2) in severity and 49 ERT-treated patients (18.7%) experienced at least one SAE. Most common SAEs were cervical cord compression (N=5, 1.9%), knee deformity (N=5, 1.9%), and developmental hip dysplasia (N=3, 1.1%), which are related to disease progression; incidence of all other SAEs was <1%.

Table 48. Summary of AEs in patients receiving elosulfase alfa (N=262)

	Incidence N (%)	Events[a]
Subjects with		
≥1 reported AE	74 (28.2%)	154
≥1 reported SAE	49 (18.7%)	69
≥1 study drug-related AE	23 (8.8%)	68
≥1 AE leading to permanent treatment discontinuation	0	0
Death		
Unrelated to ERT	5 (0.02%)	
Related to ERT	0	

Mapping was based on MedDRA version 20.0. Subjects who experience more than 1 AE within a given MedDRA system organ class or preferred term were counted once within that system organ class or preferred term.
[a]Multiple events were counted if a subject had the same AE with different onset dates or times. AEs with change of severity may be counted multiple times

23 ERT-treated patients (8.8%) experienced at least one drug-related AE. Most common were urticaria (2.3%), hypersensitivity (1.9%), nausea (1.5%), pyrexia (1.5%), and headache (1.1%); incidence of all other drug-related AE was <1%

Four SAEs in three patients were considered drug-related:

- Two Grade 2 allergic/anaphylactic reactions requiring drug interruption
- Two infusion-related reactions (one Grade 3, one Grade 2 [required drug interruption]) in the same patient
- All drug-related SAEs were resolved

Infusion interruption due to an AE was reported in two patients; one subsequently continued with the infusion following the interruption while the other did not. No patient permanently discontinued ERT due to an AE and 5 ERT-treated patients died.

Immunogenicity

All patients (N=262) developed anti-drug total antibodies (TAb) after 24 weeks of treatment, and most patients (≥ 89%) remained TAb positive throughout. Nearly all patients tested positive for neutralizing antibodies at least once (74.1% at the 5-year analysis visit)

Final remarks on the MARS safety data:

Overall, real-world results from MARS revealed no new safety concerns. These results corroborate and confirm the acceptable long-term safety profile of elosulfase alfa as observed in clinical trials.

Overall, the registry immunogenicity data, though sparse, appears to be consistent with data previously reported for the clinical trials. No correlation between antibody results and the incidence or severity of AEs was seen in the clinical trials.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

The safety data for elosulfase alfa is based on the treatment of 235 MPS IVA patients, 222 of whom are treated with the recommended dosage schedule of 2.0 mg/kg/QW. Table 49 gives an overview of the incidence with which side effects occurred in them in the MOR-005 (complete report of adverse events available in 9.7.2).

There were no side effects leading to the permanent discontinuation of the treatment and no deaths in connection with the treatment. In the randomised clinical study MOR-004, 117 patients were treated with elosulfase alfa, 59 of whom were treated with a dosage schedule of 2.0 mg/kg/QW (SPC, 2014). Of the 117 patients, 86 were exposed to elosulfase alfa for longer than 48 weeks, 52 of which took the recommended dose of 2.0 mg/kg/QW. Elosulfase alfa is also well tolerated in the longer term. Over time the frequency of the side effects decreased or remained stable with no increase in severe side effects or hypersensitivity reactions.

Most side effects related to infusion reactions, which occurred within one day of the start of the infusion. The most frequently occurring infusion reactions (≥10% with elosulfase alfa and ≥5% more than with placebo) were headache, nausea, sickness, fever, chills and abdominal pain. The infusion reactions were in general mild to moderate in nature and mainly occurred during the first 12 weeks of treatment. Severe infusion reactions may also occur, namely anaphylaxis, hypersensitivity and sickness. Recently a safety study in pediatric patients showed that after 52 weeks of treatment with elosulfase alfa the most commonly reported side-effects were pyrexia (40%) and vomiting (33%), which is similar as seen in other studies with enzyme replacement therapies (Hendriksz et al., 2014b). No patient permanently discontinued treatment due to an adverse event.

See also Table 50, which gives the side effects that are most frequent (≥5%) or severe according to the SPC (SPC, 2014).

Across studies, infusion associated reactions related to elosulfase alfa were generally mild to moderate in severity and manageable with symptomatic treatment and/or infusion rate modification. Less than 1% of infusions across clinical studies were interrupted or discontinued and required medical intervention. In MOR-004, all patients

who experienced infusion associated reactions received and tolerated subsequent infusions. Hypersensitivity adverse events did not increase in incidence or severity with time of treatment or with development of anti-drug antibodies.

Conclusion on safety profile

The adverse effects of elosulfase alfa are comparable with those of other enzyme replacement treatments. Elosulfase alfa is also well tolerated in the longer-term. Over time, the frequency of the side effects decreases or remains stable with no increase in severe side effects or hypersensitivity reactions. Most SAEs occurring during MOR-005 were related to planned surgical procedures, which were allowed in MOR-005, but not in MOR-004. There were two study-drug related SAEs which occurred in separate patients, anaphylaxis (grade 4) and haematuria (grade 2) (Hendriksz et al., 2016c). One death unrelated to elosulfase alfa occurred due to postoperative pulmonary complications secondary to diseases related events spinal cord compression, laminectomy, and spinal fusion. Most side effects relate to infusion reactions that are generally mild to moderate in nature. These are primarily headache, nausea, sickness, fever, chills and abdominal pain. However, severe infusion reactions may also occur, in particular anaphylaxis, hypersensitivity and sickness. In the clinical studies to date this has not resulted in any deaths or in the definitive premature discontinuation of the treatment (Hendriksz et al., 2016c).

In addition, real-world results from the MAA and from MARS revealed no new safety concerns, as described in the previous section. These results corroborate and confirm the acceptable long-term safety profile of elosulfase alfa as observed in clinical trials.

Table 49. Overall summary of adverse events during MOR-005 (ITT population)

	PBO-QW (N=29)	QW-QW (N=56)
Any AE, N (%)	29 (100.0%)	56 (100.0%)
Number of AEs per patient, N Mean Median	 24.9 18.0	 35.9 26.5
Any study drug-related AE, N (%)	20 (69.0%)	43 (76.8%)
Any SAE, N (%)	14 (48.3%)	23 (41.1%)
Number of SAEs per subject, N Mean Median	 0.7 0.0	 0.7 0.0
Any study drug-related SAE, N (%)	0 (0%)	0 (0%)

Any AE leading to permanent study drug discontinuation, N (%)	0 (0%)	1 (1.8%)
Death, N (%)	0 (0%)	0 (0%)

AE: adverse event; SAE: serious adverse event (Hendriksz, Parini et al., 2016b)

Table 50. Adverse effects of elosulfase alfa most common or severe according to the SPC

Most frequent (≥5%)	Headache Dizziness Shortness of breath Diarrhoea, sickness, oropharyngeal pain, (upper) abdominal pain, nausea Muscle pain Chills Fever
Severe	Anaphylaxis Hypersensitivity, sickness

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Outcomes from the 'parent-child' studies, MOR-004/-005 and MOR-002/100 have been integrated using a variety of statistical analyses and methods. Further details on these analyses are provided in the clinical study reports for MOR-005 and MOR-100, respectively. Beyond that, no other evidence synthesis or meta-analysis has been undertaken, beyond a focus on the relevant populations for analysis as below.

Evidence synthesis is driven by the complexity of the disease and ethical concerns in subjecting these patients to a clinical study. The MOR-004 pivotal study duration was limited to 24 weeks due to ethical concerns on withdrawing patients' access to surgery for a longer duration. However, in this study, significance versus placebo was met in the most sensitive primary outcome measure. As with other ERTs for MPS diseases, secondary and tertiary outcomes take longer to develop – typically 2-3 years.

The MOR-004 population continued to be studied in the MOR-005 extension study, with the protocol describing a switching to the indicated dose and the patients being able to access surgery. Due to the relevance of the 2mg/kg/QW indicated dose this is

considered the relevant population to follow and it is considered important to consider this population's results without the confounding effects of surgery. Hence, in analysis, the per protocol group from this arm is considered most relevant.

In consideration of the short duration of the placebo arm and the enhanced care, it was considered that the most relevant comparative arm in terms of standard clinical practice without elosulfase alfa would be the longitudinal analysis of the MOR-001 (MorCAP) study. This data was reanalysed to focus on a population that matched the MOR-004 inclusion criteria and represented a relevant cohort for comparison.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

As explained in section 9.8.1 above, apart from the integrated analysis of outcomes in the MOR-004/-005 and MOR-002/100 studies, evidence synthesis is not considered appropriate or methodologically possible due to the heterogeneity of the studies and their design: in particular, differences in the populations studied, the inclusion and exclusion criteria, study duration, endpoints, and different study arms.

The overall results of the individual studies are described qualitatively below:

MOR-004: pivotal trial

For a reminder of the study design and methodology, please refer to Table 16.

Overall, the results from the phase 3 study (MOR-004) demonstrate the clinical efficacy of elosulfase alfa in MPS IVA patients. Efficacy results confirmed that a dose of 2.0 mg/kg/week met the primary endpoint and statistically significantly (P=0.0174) improved 6MWT distance compared with placebo at week 24. Both elosulfase alfa regimens led to a reduction in urine KS, a pharmacodynamics biomarker of disease. Results from the other outcome measures (3MSCT, respiratory function, and quality of life assessments) were not statistically significant but did show a trend towards an improvement compared to placebo. The other outcomes did not achieve the statistical significance due the limited duration of the trial (Hendriksz et al., 2014b).

Additional efficacy findings from MOR-004 showed numerical improvement across nearly all secondary and tertiary endpoints captured in the study.

Overall, the results of this study demonstrate a favourable benefit/risk profile for elosulfase alfa. Improvement over placebo in 6MWT distance was observed as early as Week 12, with further improvement at Week 24 suggesting a continuing upward trajectory in 6MWT improvement.

MOR-004 data show an increase in wheelchair use in patients on placebo as expected, since the progressive nature of the disease (Harmatz et al., 2013) and the lack of a similar increase in wheelchair use amongst patients on active treatment is notable and may be clinically relevant in light of the progressive nature of MPS IVA.

Because MPS IVA is a multi-systemic disease with multifaceted impairments, other parameters were included to evaluate endurance, respiratory function, urine KS, growth, and subjective health assessments. Results from these parameters directionally supported the primary endpoint and the weekly dose regimen and taken together provide supportive evidence for improvement in a

wide range of disease-related manifestations. Stringent quality measures, thorough training of sites and Investigators, and vigorous data monitoring resulted in robust, high-quality data.

Overall, this large double-blind placebo-controlled pivotal trial provides strong evidence of improvement in health and function of MPS IVA patients treated with elosulfase alfa (Hendriksz et al., 2014b).

MOR-005: extension of pivotal trial MOR-004

For a description of the study design and methodology, please refer to **Error! Reference source not found.**, and for baseline c haracteristics, see Table 16.

The results have shown patients experience a sustained improvement in the 6MWT and show continued improvement in the 3MSCT and across pulmonary function measures. Patients also showed a prolonged reduction in the pharmacodynamic biomarker urine keratan sulfate. These measures are statistically significant and clinically meaningful when compared to the similar untreated natural history cohort. The natural history cohort highlights the progressive nature of the disease with deterioration in endurance and pulmonary function observed.

6MWT results

Mean (SE) change from baseline to Week 120 in 6MWT distance was 39.9 metres (10.1) m for patients receiving elosulfase alfa at 2.0 mg/kg/QW throughout the study (QW-QW, N=56) for the MPP populations (see Table 51). Additional analyses revealed that

durability of 6MWT improvements was not impacted by baseline 6MWT distance, use of a walking aid, or age (Hendriksz et al., 2016c).

Given that 6MWT values for MPS IVA patients are very low (about 200m), even small improvements in these patients would result in dramatic improvements in the ability for patients to do routine daily tasks such as being able to go to the toilet on their own and be less dependent on caregivers for support. Nevertheless, the improvement from baseline in 6MWT after 24 weeks in the elosulfase alfa 2.0mg/kg/week arm was 36.5m which represents a 17.3% improvement in baseline. These improvements are amongst some of the largest improvements that have been reported in enzyme replacement therapies over a similar time frame. Furthermore, these improvements have been shown to continue to develop overtime, with the results from the MOR-005 Phase 3 extension study, showing an improvement in 6MWT from baseline of 46.0m at Week 72 and maintained through to Week 120 (Figure 33).

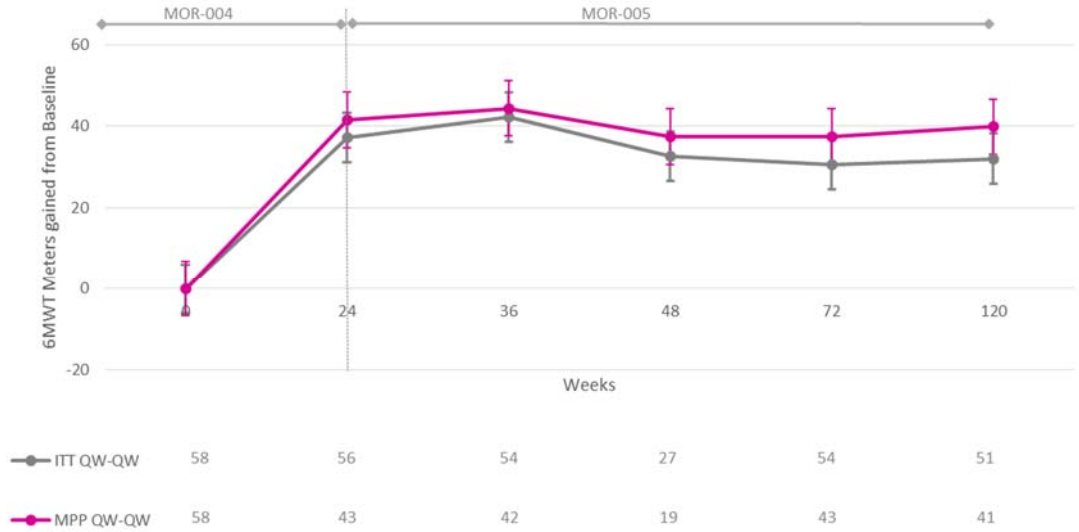
Table 51. MOR-005 long term follow-up for 6MWT in the MPP QW QW population

	Year 1[a]		Year 2[b]	
	MOR-001	QW-QW	MOR-001	QW-QW
MPP Population/MOR-001				
6MWT (m), N	67	43	27	41
LS mean change from baseline[c] (SE)[d]	-6.7 (8.78)	38.5 (11.02)	-21.9	39.0 (11.32)
P-value[e] for difference from MOR-001		0.0016	(12.30)	0.0003

[a]Year 1 represents data collected from the MOR-004/005 Week 72 assessment and the MOR-001 Year 1 follow-up window
[b]Year 2 represents data collected from the MOR-004/005 Week 120 assessment and the MOR-001 Year 2 follow-up
[c]Baseline LS means are based on ANCOVA of baseline measurement with model terms treatment age group, and 6MWT distance category
[d]LS mean changes based on repeated measures ANCOVA model including treatment, time point, treatment and time point interaction, age group, and baseline 6MWT category, and baseline measurement (3MSCT and uKS only)

[e]P-value determined by t-test and the repeated measures ANCOVA model
LS: least square; SE: standard error

Figure 33. Change in 6MWT from baseline over 120 weeks



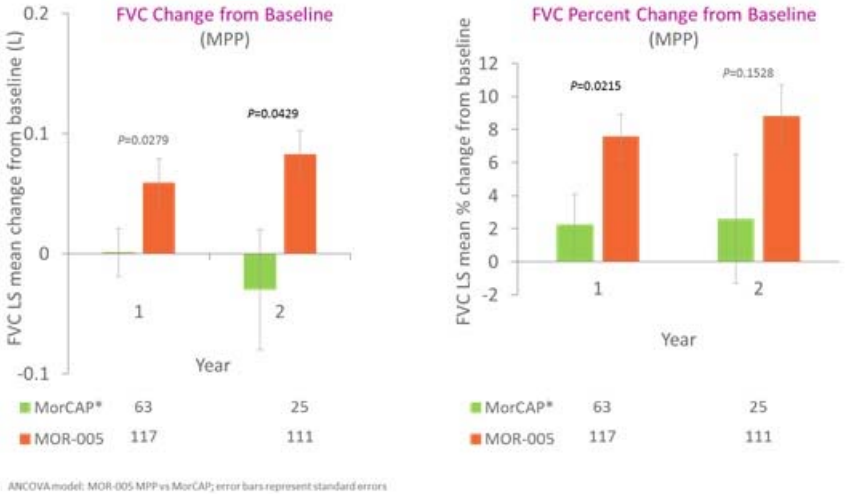
Source: Hendriksz, Parini et al, 2016a.

Lung function results

After 120 weeks, the mean change from baseline in FVC was 0.087 (SE 0.021) and a mean improvement of 9.2% (SE 1.9%). The results were similar at 120 weeks for FEV1, showing a mean change from baseline of 0.065 (SE 0.019) and a mean improvement of 8.8% (SE 2.3). The mean change in MVV at 120 weeks was 1.84 (SE 1.21) with a 6.1% change from baseline.

An ANCOVA analysis demonstrated significant improvements from baseline in the MOR-005 population versus corresponding untreated patients in the MOR-001 study for FVC, FEV1 and MVV at both 1 and 2 years (P<0.05) (See Figures 34-36 below). The Least Squares mean changes from MOR-004 baseline were +0.0827 L (8.8%) at 120 weeks, compared to -0.0299 L (2.6%) in MOR-001. Lung function improves under long-term treatment with elosulfase alfa in line with what is observed under other enzyme replacement therapies.

Figure 34. MOR-005 FVC change from baseline and percent change from baseline compared to MOR-001



Source: Hendriksz, Berger et al, 2016b

Figure 35. MOR-005 FEV1 change from baseline and percent change from baseline compared to MOR-001
Source: Hendriksz, Berger et al, 2016b

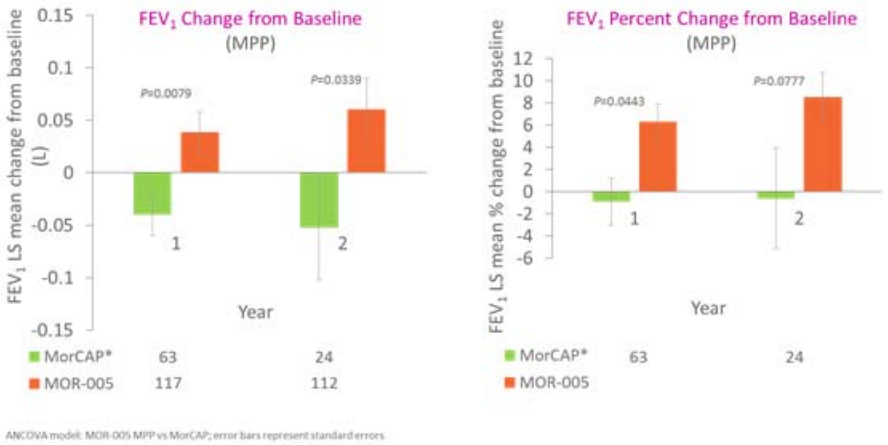
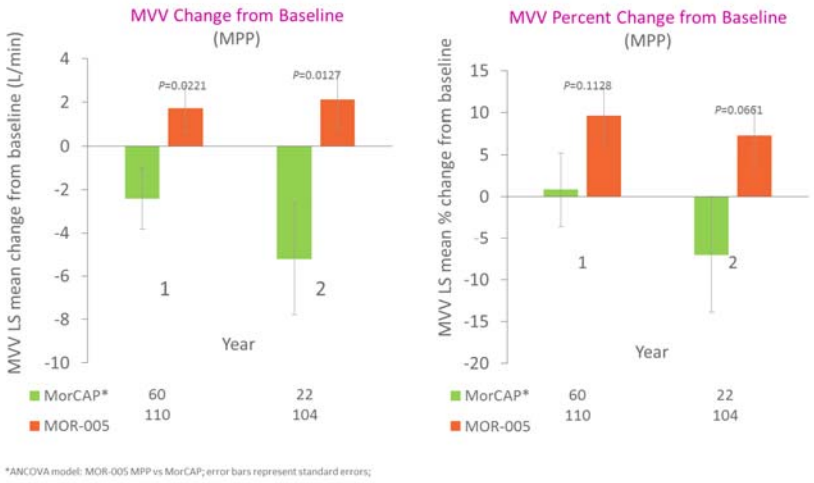


Figure 36. MOR-005 MVV change from baseline and percent change from baseline compared to MOR-001



*ANCOVA model: MOR-005 MPP vs MorCAP; error bars represent standard errors;

Source: Hendriksz, Berger et al, 2016

3MSCT results

In the relevant MPP QW-QW population of patients receiving elosulfase alfa at 2.0 mg/kg/wk the mean (SE) change at Week 120 over baseline in the 3MSCT was 6.2 (2.24) stairs/min. For 3MSCT results, which did not reach significance during MOR-004 24-week study, statistical significance was achieved in the MOR-005 study in the MPP populations versus the MOR-001 subpopulation ($P<0.05$; See Table 52). The more gradual course of 3MSCT improvement, as compared to 6MWT improvement, is noteworthy and may indicate that the 3MSCT is less sensitive to shorter term treatment effects than the 6MWT in Morquio A patients. This may be due to the increased challenge stair-climbing poses for Morquio A patients in comparison to walking in the 6MWT, due to extremely short stature and disease involvement of the ankles, knees, and hips, as well as the upper extremities which aid in stair climbing via the handrail.

Table 52. MOR-005 long term follow-up for 3MSCT in the MPP QW/QW population

	Year 1[a]		Year 2[b]	
	MOR-001	QW-QW	MOR-001	QW-QW
MPP Population/MOR-001 2				
3MSCT (stairs/min), N	67	43	27	41
LS mean change from baseline[c] (SE)[d]	0.5 (1.51)	5.5 (1.85)	-1.2 (2.39)	6.2 (2.24)
P-value[e] for difference from MOR-001		0.0375		0.0236

[a]Year 1 represents data collected from the MOR-004/005 Week 72 assessment and the MOR-001 Year 1 follow-up window
[b]Year 2 represents data collected from the MOR-004/005 Week 120 assessment and the MOR-001 Year 2 follow-up
[c]Baseline LS means are based on ANCOVA of baseline measurement with model terms treatment age group, and 6MWT distance category
[d]LS mean changes based on repeated measures ANCOVA model including treatment, time point, treatment and time point interaction, age group, and baseline 6MWT category, and baseline measurement (3MSCT and uKS only)
[e]P-value determined by t-test and the repeated measures ANCOVA model
LS: least square; SE: standard error

Keratan sulfate concentration in urine

The mean change in KS concentration in urine from baseline at week 120 was -63.8 (SE 7.47) in the QW-QW population. Reductions in uKS were seen regardless of age cohort. When compared to MOR-001 patients at approximately 2 years follow-up (uKS=+6.2 [SE 8.46]), ANCOVA analysis showed a significant difference ($p<0.0001$) in uKS levels.

MPS HAQ results, including changes in wheelchair use (Hendriksz *et al.*, 2017)

The MPS HAQ, originally developed for MPS I, was used to measure activities of daily living in both MOR-001 and MOR-004/005 (further information is provided in the annex). As part of the Phase 3 trial programme (MOR-004) and the extension trial (MOR-005), three domains of the MPS HAQ was administered to patients or their caregivers:

- Self-care:
    - Eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting
- Mobility:
    - Dexterity, mobility, walking, stair climbing, and gross motor skills
- Caregiver assistance

Level of caregiver assistance required in eating, grooming, bathing, dressing, toileting, transfers, and locomotion. Range total domain score 13 (independent) to 52 (complete assistance required)

For the Self-care and Mobility domains, patients were asked to respond via a Likert scale ranging from 0 (not difficult at all) to 10 (extremely difficult). If a patient was unable to do, a score of 11 was recorded. The sums of responses were divided by the number of questions answered. The baseline characteristics can be seen in Table 53.

Table 53. Baseline characteristics for those patients with valid MPS-HAQ results

	MOR-005 ITT All N=169a	MOR-005 ITT QW-QW N=55	MorCAP N=94
Age, years; median (range)	11.7 (5.0-57.4)	10.0 (5.0-41.9)	11.9 (5.0-65.6)

Gender, % Male Female	50.3 % 49.7%	47.3% 52.7%	42.6% 57.4%
Height, cm; median (range)	99.6 (81.0-165.0)	98.7 (82.7-141.4)	102.0 (83.0-150.5)

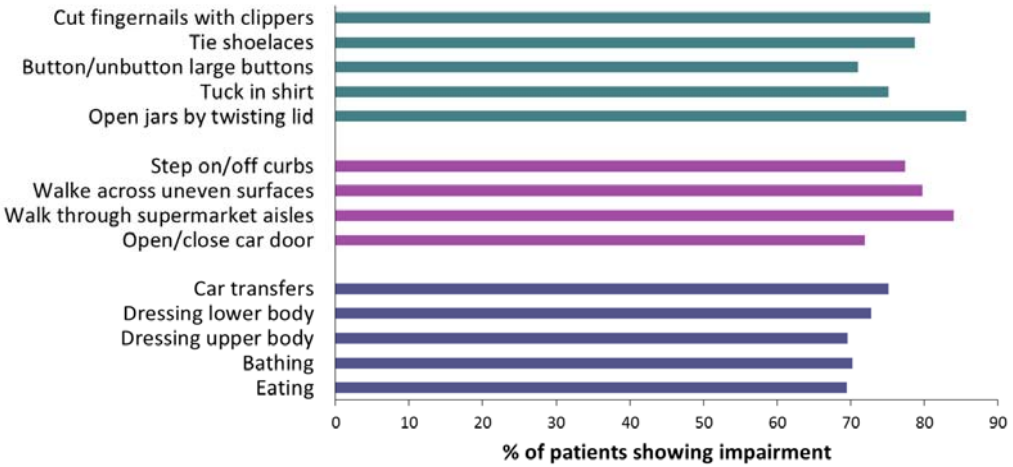
An ANCOVA analysis was conducted comparing the MOR-005 ITT, MOR-005 ITT QW-QW, and a similar population from the MorCAP study at one and two years.

Figure 37 provides an overview of the items in the scale which patients had trouble doing at baseline. It is clear that the vast majority of patients had significant impairments at the start of the study.

Figure 38 provides the results of the Self-Care domain analysis. The Least Squares mean difference of the ITT population from MorCAP at 2 years was -0.7 (SE 0.3, p=0.0146), indicating that even in the ITT population, self-care improved over time when compared with a natural history cohort. The impact is even more pronounced in those patients who received the correct dose from baseline.

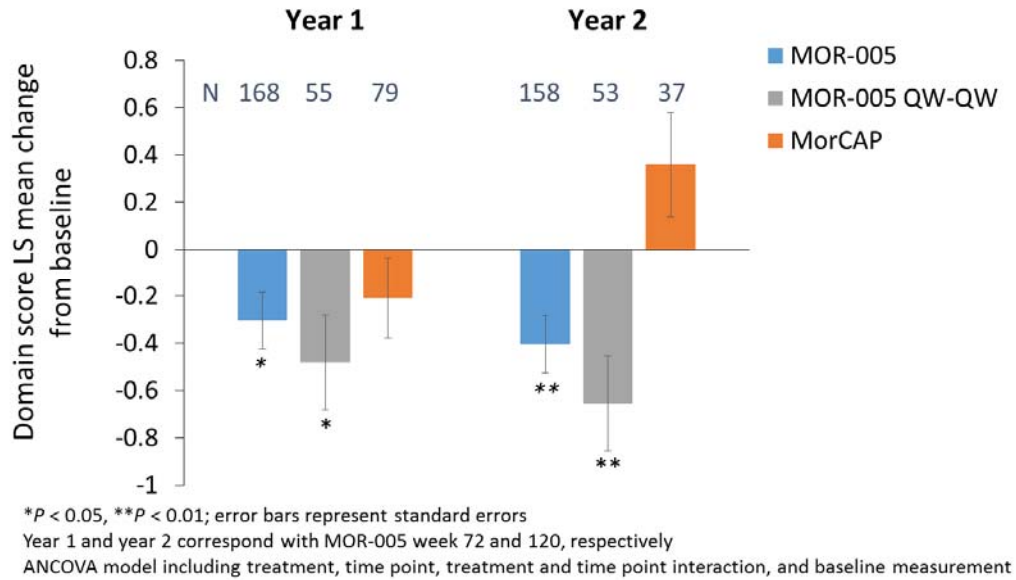
The results of the Caregiver assistance domain are shown in Figure 37. MPS HAQ items showing impairments (score<1) at baseline. The scores decreased (indicating improvement) more at 2 years with elosulfase alfa than in untreated patients, with the best improvements seen in those patients who were on the correct dosing regimen. Although not shown here, when compared to those patients who were compliant and did not have surgery (the MPP population), the change in caregiver domain was significantly different from untreated patients. In addition, only those patients with a caregiver assistance baseline score above the mean showed significant improvements versus baseline at year 1 and 2, suggesting a potential ceiling effect.

Figure 37. MPS HAQ items showing impairments (score<1) at baseline



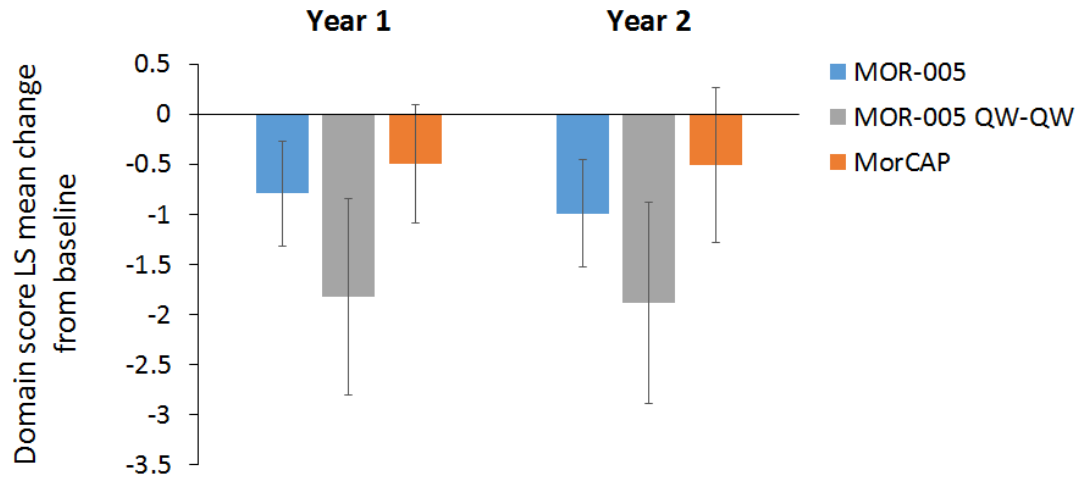
Source: Harmatz et al, 2013.

Figure 38. Self-care Domain change from baseline at 1 and 2 years



(Hendriksz *et al.*, 2018)

Figure 39. Caregiver assistance domain change from baseline at 1 and 2 years

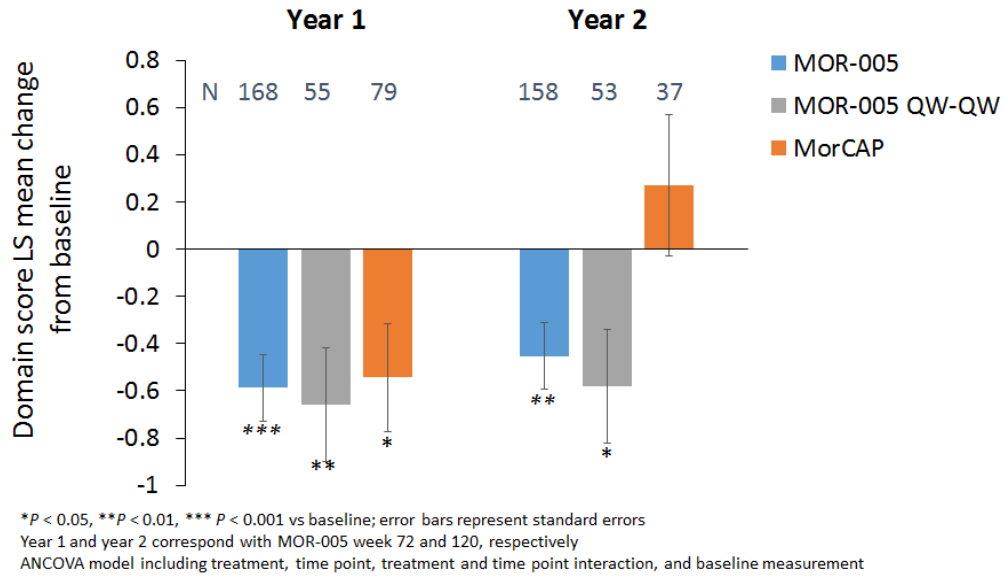


Error bars represent standard errors
Year 1 and year 2 correspond with MOR-005 week 72 and 120, respectively
ANCOVA model including treatment, time point, treatment and time point interaction, and baseline measurement

(Hendriksz *et al.*, 2018)

Figure 40 provides the results of the mobility domain, showing that over time, treated patients were significantly better (ITT -0.7 [SE 0.4, p=0.0490]) than an untreated population, with the QW-QW patients tending to have better scores than the ITT population.

Figure 40. Mobility Domain change from baseline at 1 and 2 years



(Hendriksz *et al.*, 2018)

A comparison of the results of the MOR 005 study in week 120 with those obtained from the MOR-001 study (two years) shows that the treatment of MPS IVA with elosulfase alfa reduces the degree of progression of the disease and wheelchair dependency (Table 54). After 120 weeks of treatment with elosulfase alfa, 40% of the patients in the MOR-005 study said that they were less dependent on their wheelchair, compared with 16.7% of those in the untreated historical control group over the same period. This reduction was defined as the transition from constant wheelchair use at the start of the study to occasional wheelchair use at the end of the study period. Only 13.6% of the patients treated with elosulfase alfa in the MOR-005 study reported increased wheelchair use compared with 24% in the untreated historical control group over a comparable period. This increase was defined as the transition from occasional wheelchair use at the start of the study to constant wheelchair use at the end of the study. Taken

together, these results show that elosulfase alfa reduces the progress of the disease and that improvements in endurance translate into a reduction in wheelchair dependency, which leads to an increase in quality of life and greater independence.

Table 54. Change in wheelchair use after 120 weeks of treatment with 2.0 mg/kg/QW of elosulfase alfa compared to MOR-001

	Wheelchair health state at Baseline		
Wheelchair health state at week 120 (MOR-005)	No WC	Occ. WC	Always WC
No WC	80.8%	13.6%	0%
Occ. WC	15.4%	72.7%	40%
Always WC	3.8%	13.6%	60%

	Wheelchair health state at Baseline		
Wheelchair health state at 2 years (MOR-001)	No WC	Occ. WC	Always WC
No WC	78.9%	3.4%	0%
Occ. WC	21.1%	72.4%	16.7%
Always WC	0%	24.1%	83.3%

According to the EPAR: 'As the disease impacts different organs, multiple clinically relevant endpoints are of importance in terms of providing further support for clinical efficacy. Overall, secondary endpoints show a trend for improvement. The results of the 3MSCT support the efficacy of weekly injections in contrast to every other week injections. Other endpoints like respiratory function and anthropometric measures also showed an improvement with 2.0 mg/kg/qw elosulfase alfa, supporting the primary outcome. This was further supported by results of the MPS Health assessment questionnaire, although not all domains showed an improvement. Additional analyses showed an increase in wheelchair use observed in the placebo group (n=5) that was not seen in the treated arms (n=0) at week 24. Additional data on QoL and clinical improvements indicate a benefit. Further the incidence of orthopaedic surgery is in favour of the elosulfase alfa treated patients. After 72 weeks treatment about 8% of the patients on elosulfase alfa treatment and about 18% had undergone orthopaedic surgery. A further analysis of the ADL items from the HAQ showed some improvement after 24 weeks treatment with most notably the improved ability to dress, go to the toilet, independent eating and drinking and the ability to get on and off furniture.'

The MOR-004/005 MPS-HAQ baseline data showed that Morquio A has a negative impact on the patients' ability to perform activities of daily living, which confirms results from previous studies. Elosulfase alfa treatment was associated with a reversal of the natural deterioration in functional capacity known to occur in Morquio A for at least two years. There were improvements in all MPS-HAQ domains tested, with the greatest improvements seen in patients receiving the recommended weekly dosing regimen. These improvements were significantly greater than a comparable, untreated population, which generally saw declines or no improvements over two years.

Conclusions

Elosulfase alfa is the first and only therapy that treats the underlying cause, counteracts the progress of the disease and improves the functional status and quality of life in patients of all ages with the very rare, disabling condition MPS IVA. Endurance increases with a significant improvement in the 6MWT after only 24 weeks. Patients in MOR-004 also experienced an improvement in the performance of a number of activities of daily living at 24 weeks, as well as an improvement in quality of life and a reduction in the amount of informal care required.

The MOR-005 extension study showed a continuous improvement after 120 weeks of treatment in endurance and/or pulmonary function for all patients, a reduction in wheelchair dependency and a reduction or deferral of surgical interventions.

In the absence of a placebo control in the extension phase, these data must be interpreted with some caution, but the observed long-term durability of effect is clinically meaningful given that progressive decline in endurance and overall function are expected as part of the natural history of patients with MPS IVA.

MOR-002: dose-escalation study and its MOR-100 extension

Please refer to Table 17 and

Table 18 for a description of methodology and baseline characteristics.

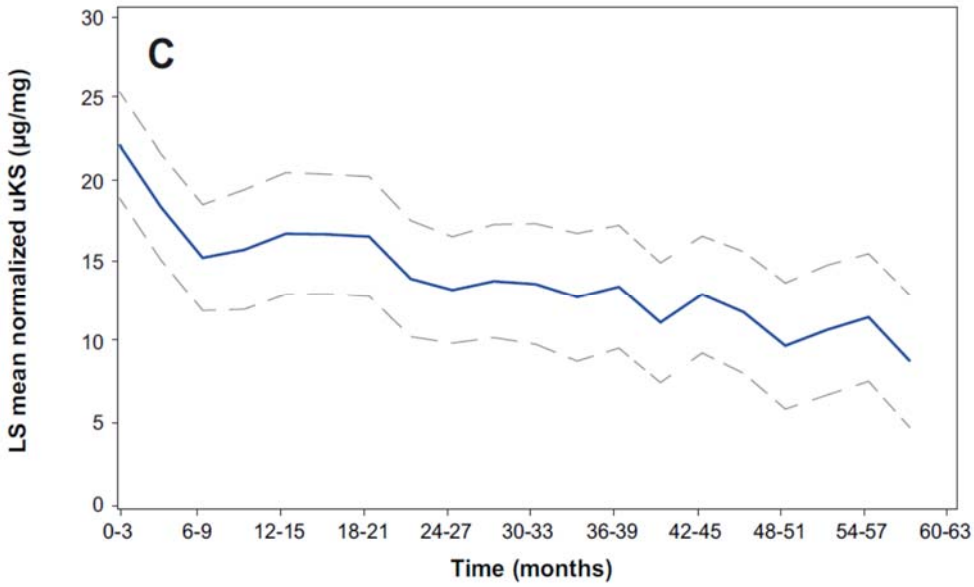
Results of the MOR-002 and MOR-100 studies

Urinary keratan sulfate (uKS)

In the course of the MOR-002 trial, the uKS decreased significantly in dose-dependent manner in response to the increase in the elosulfase alfa dose. The mean value of uKS was reduced by 35.1 (± 38.19%) in week 72.

The overall trend in uKS was analysed by mixed-model analysis at 3-month intervals. Figure 41 illustrates the declining trend in LS mean uKS over the course of MOR-002 and MOR-100.

Figure 41. MOR-002 and MOR-100. Least squares mean normalized urine keratan sulfate (uKS; µg/mg) by month.

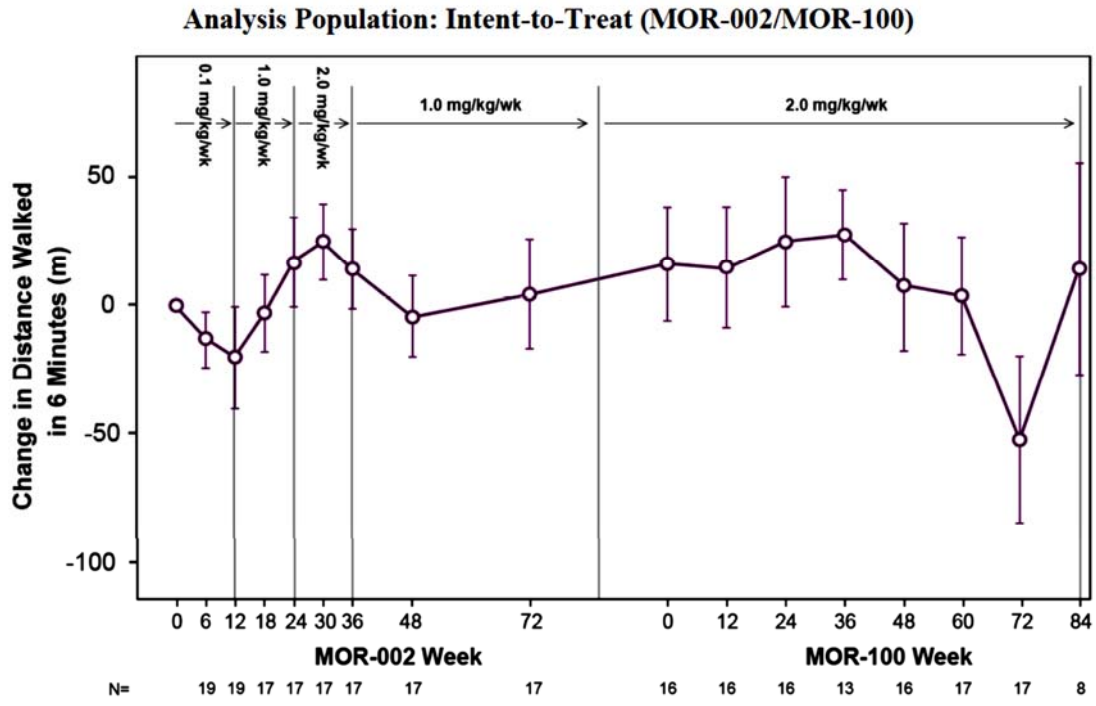


Dashed lines represent the 95% CI. Least squares (LS) mean is based on mixed-model analysis performed with outcomes modelled at 3-month intervals with repeated measures for patients and months.

Measurements of endurance

Compared with baseline the patients exhibited a positive mean and median variation of the distance walked in the course of the 6MWT for the two treatment phases with the 2 highest dosages (1.0 and 2.0 mg/kg/week) (Figure 42).

Figure 42. Variation, compared with baseline, of the mean distance (SD) walked during the 6MWT – Total follow-up duration of 156 weeks - MOR-002 and MOR-100 trials (Biomarin, 2013)

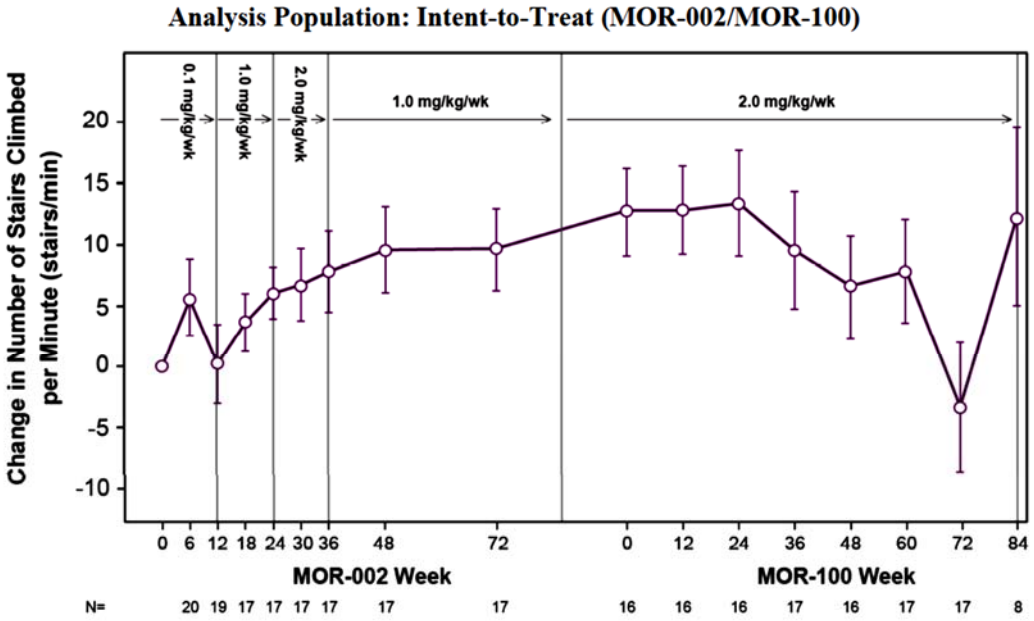


N = number of subjects at each time point
Note: Error bar refers to standard error.

The mean distance walked in the course of the 6MWT decreased greatly in week 72 (-52.7m), because 4 patients had undergone knee surgery – a common procedure in patients suffering from MPS IVA – just before this visit. These patients exhibited a decrease of >150 m in their walking distance compared with their previous evaluation.

Compared with baseline the endurance measured by the 3MSCT improved during the treatment phases with the 2 highest dosages (1.0 and 2.0 mg/kg/week) but not with the lowest dose (0.1 mg/kg/week). Both the median and mean variations of the number of stairs climbed per minute increased with increasing dose of elosulfase alfa (Figure 43). This improvement was continuous.

Figure 43. Variation, compared with inclusion, of the mean number (SD) of stairs climbed per minute during the 3MSCT – MOR-002 MOR-100 trials – ITT population (Biomarin, 2013)



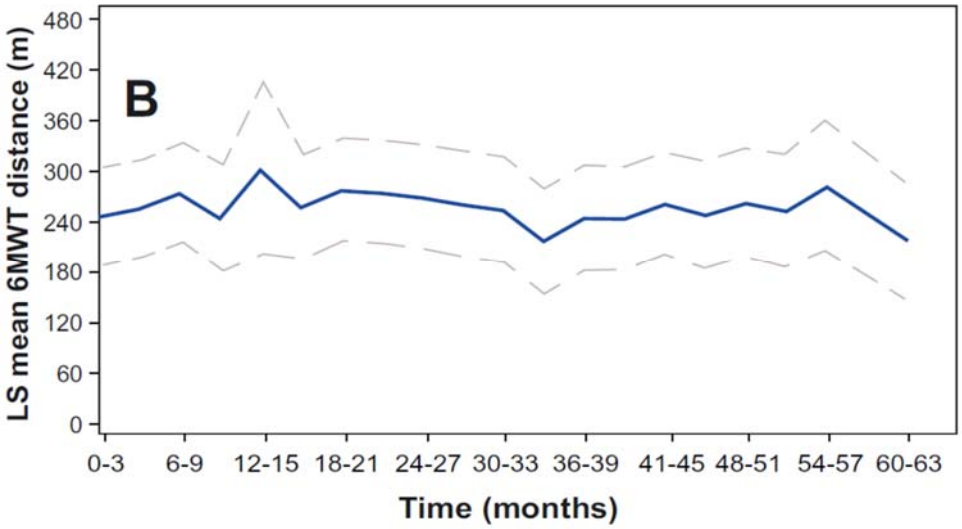
N = number of subjects at each time point
Note: Error bar refers to standard error.

The causes of the large decrease in the number of stairs climbed during the 3MSCT in week 72 were identical to those cited for the 6MWT.

To analyse the long-term 6MWT outcomes, a mixed-model analysis of the combined MOR-002/MOR-100 dataset was performed over 3-month intervals and showed no significant trend toward decline over 5 years, with the least squares mean distance remaining stable at approximately 270 m (

Figure 44). The downward trend in natural history data where patients see an annual decline of 6.8m, suggest that the stability observed in MOR-002/100 patients after 5 years would have been unlikely in the absence of treatment.

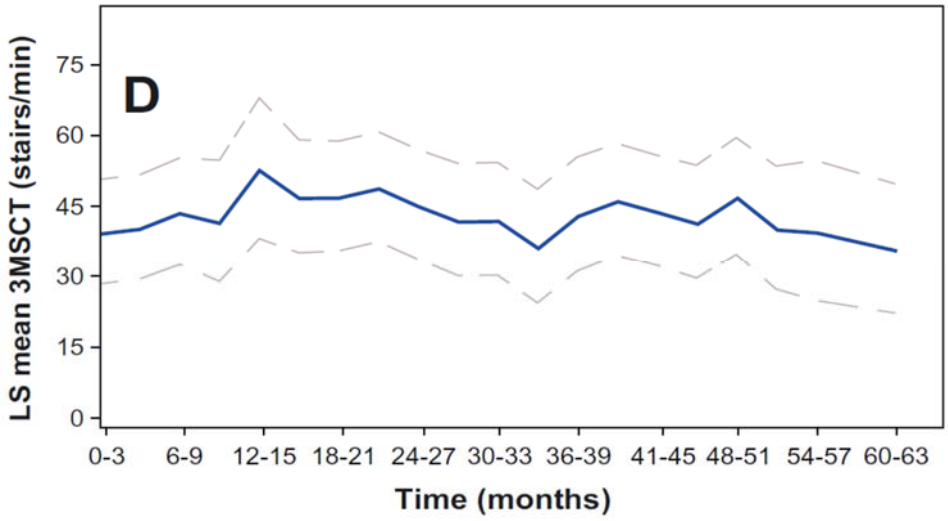
Figure 44. MOR-002/MOR-100 combined LS mean 6MWT (m) by months of treatment exposure.



Dashed lines represent the 95% CI. LS means are based on mixed-model analysis performed with outcomes modelled at 3-month intervals with repeated measures for patients and months.

Similar to the 6MWT, the least squares mean rate remained relatively stable over 5 years at approximately 37 stairs/min, with no trend toward decline (Figure 45).

Figure 45. MOR-002/MOR-100 combined LS mean 3MSCT rate (stairs/min) by months of treatment exposure.



Dashed lines represent the 95% CI. LS means are based on mixed-model analysis performed with outcomes modelled at 3-month intervals with repeated measures for patients and months.

Respiratory function

Compared with baseline, an improvement of 10.1 (± 27.83%) of the FVC and of 16.1 (± 21.96%) of the MVV was observed in week 36 (Figure 46). After approximately 2 years of treatment, the FVC exhibited a continuous improvement with a mean increase of 15.3% compared with baseline (

Figure 47).

In addition, the results of these 2 studies showed that the MVV is more sensitive to a treatment for 24 weeks, whereas the improvement of the FVC seems to require longer treatment duration.

Figure 46. Mean variation (SE) of the MVV compared with inclusion – ITT population - MOR-002 and MOR-100 trials

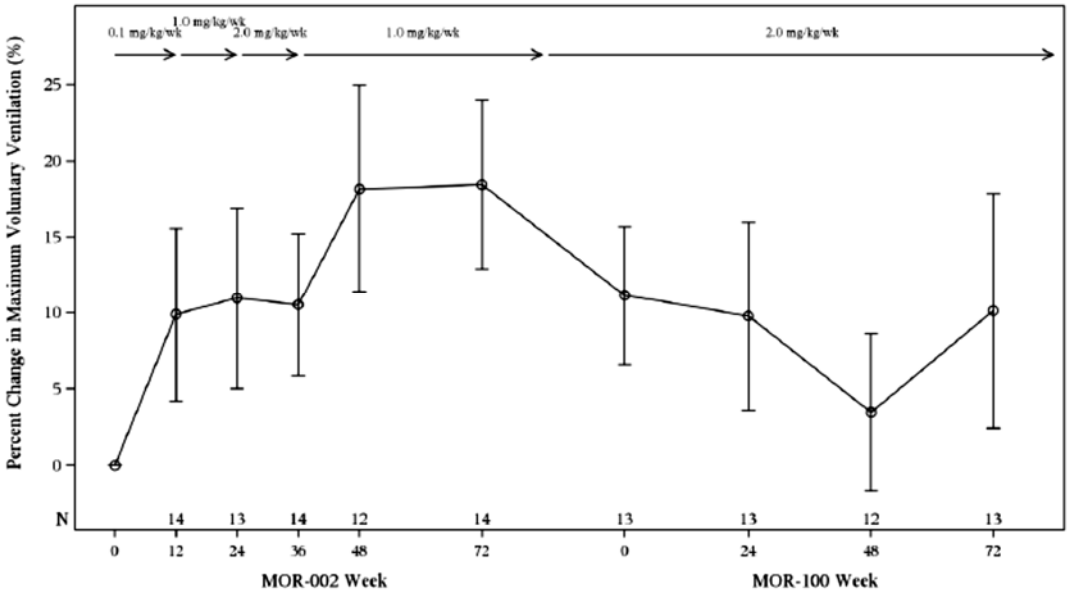
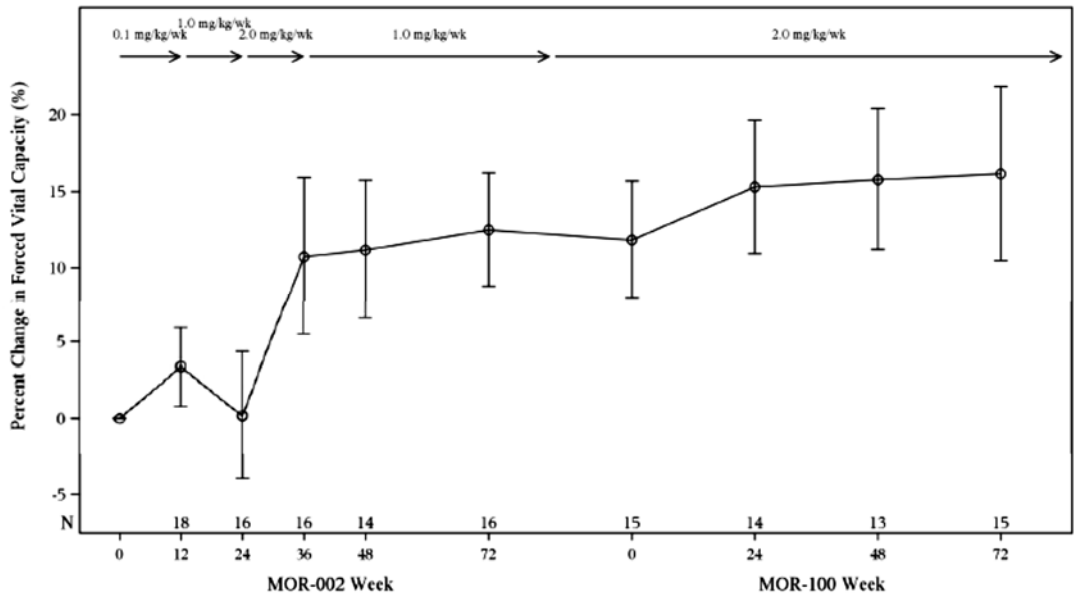


Figure 47. Mean variation (SE) of the FVC compared with inclusion – ITT population - MOR-002 and MOR-100 trials

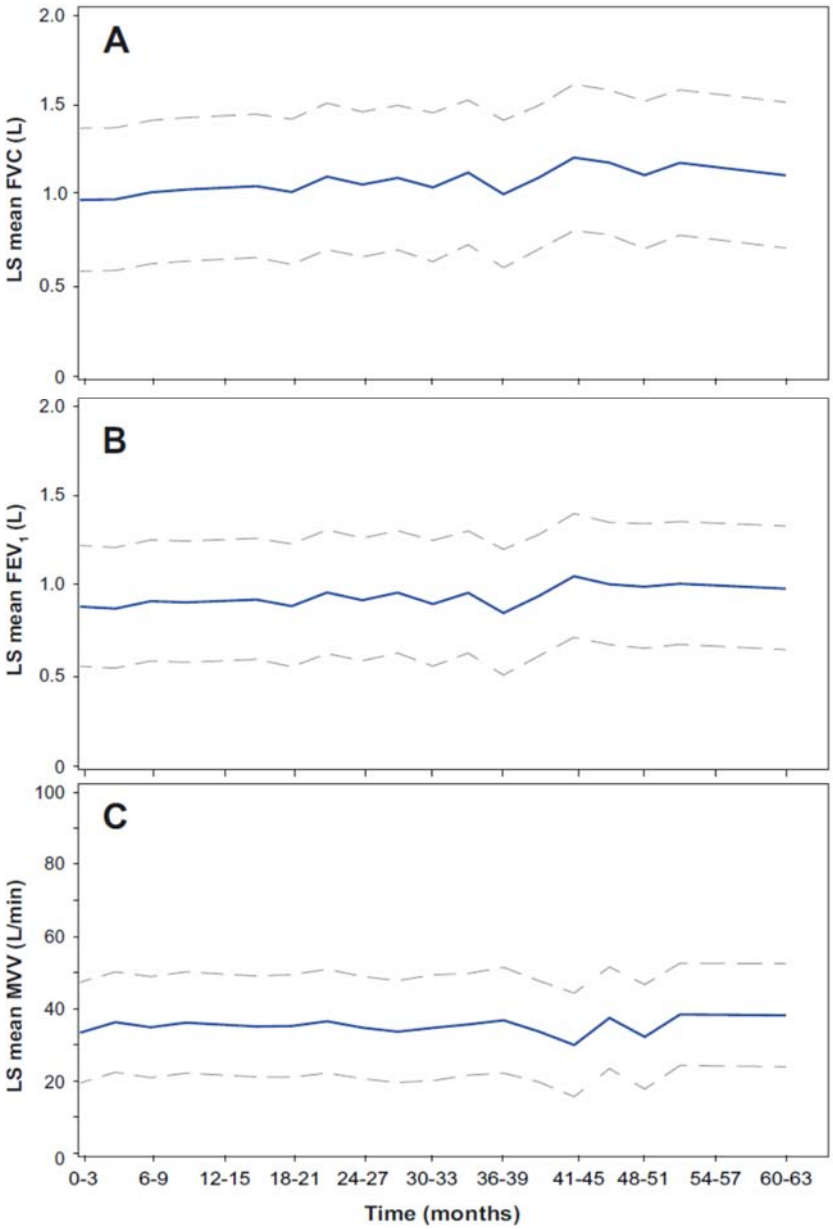


Overall, no dose-related trends in respiratory function emerged in MOR-002.

All assessments improved relative to baseline at all time points over 5 years (

Figure 48).

Figure 48. Least squares (LS) mean change in lung function by months of treatment exposure for the MOR-002/MOR-00 combined data set



(A) forced vital capacity (FVC), (B) forced expiratory volume in 1 s (FEV1), and (C) maximum voluntary ventilation (MVV) by months of treatment exposure for the MOR-002/MOR-100 combined data set. Dashed lines represent the 95% CI. LS means are based on mixed-model analysis performed with outcomes modeled at 3-month intervals with repeated measures for patients and months.

Safety

The safety population analysis included patients who received ≥1 dose of elosulfase alfa. Over the course of MOR-002 and MOR-100, all patients experienced ≥1 adverse event (AE), with most being mild or moderate in severity. The most common AEs determined by study investigators to be

possibly or probably related to study drug were pyrexia (45.0%), headache (40.0%), and increased total IgE levels (30.0%)

The majority of SAEs were consistent with complications of Morquio A syndrome and difficulties with cannulation. The most common study drug-related SAEs were injection site reactions (10.0%) and pyrexia (10.0%); the majority of remaining SAEs were primarily a result of hypersensitivity reactions. The incidence of AEs and SAEs did not appear to increase in frequency with increased dose or exposure time, regardless of whether they were determined to be related or unrelated to the study drug.

Conclusions

Among patients suffering from MPS IVA syndrome and treated by elosulfase alfa, the results of the MOR-002 ascending dose trial and of its extension phase, MOR-100, showed:

- An improvement of endurance and respiratory functions in the course of the ascending dose phase of 36 weeks, persisting in the course of the 5 years of treatment;
- A continuous improvement of the respiratory function tests;
- A dose-dependent and persistent decrease of the urinary concentration of KS.

MOR-006: clinical trial in patients with limited mobility

For a description of study MOR-006, please refer to Table 19.

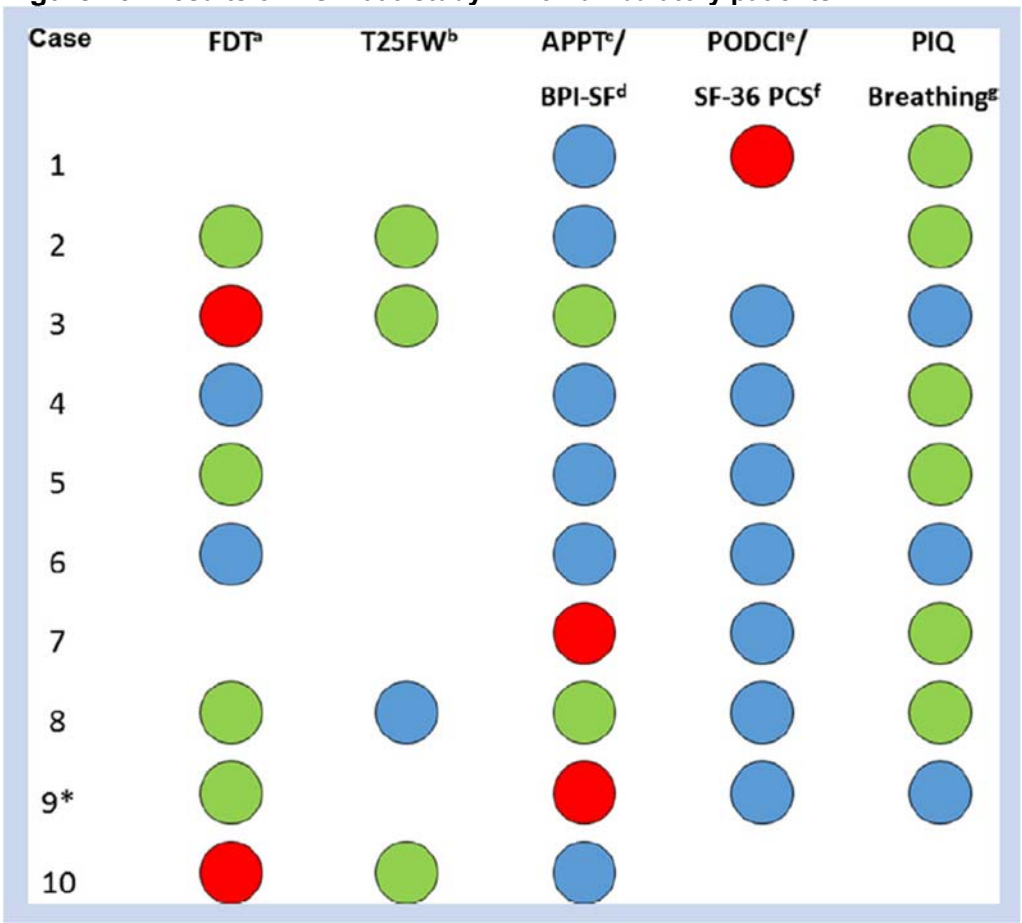
Efficacy Results

Treatment with elosulfase alfa led to a rapid and sustained decrease in urine KS. At week 48, urine KS normalized for creatinine had decreased by a mean (SE) of 52.4 (3.8) % in the MPP population.

Figure 49gives an overview of outcomes of efficacy measures at week 48 versus baseline in the MPP population. All patients remained stable or

improved in multiple outcomes. Half of the patients did not show worsening in any of the outcomes. Improvements in patient reported breathing ability (PIQ), FDT, and T25FW occurred most frequently. Eight patients showed improvements in one or more outcome measures, and several patients indicated improvements that were not captured by study assessments such as increased energy and functional ability. Figure 49 shows the results across the various assessments for each patient. The adverse events were similar to those seen in other elosulfase alfa studies. The study authors suggest that these results indicate that MPS IVA patients should be assessed on an individual basis to determine the impact of treatment.

Figure 49. Results of MOR-006 study in non-ambulatory patients



Green = Improvement, Blue = stability, Red = decline.
a) Functional Dexterity Test (FDT) improvement, increase ≥1 pegs/min ; stable, change <1 pegs/min ; worsening, decrease ≥1 pegs/min.
b) Twenty-five foot walk test (T25FW) improvement, increase speed of ≥10% ; stable, change speed <10% ; worsening, decrease speed ≥10%.
c) Adolescent and pediatric pain tool (APPT) pain intensity (Word Graphic Rating Scale) improvement, decrease ≥1 point ; stable, change <1 point ; worsening, increase ≥1 point.
d) Brief Pain Index short form (BPI-SF) pain intensity improvement, decrease ≥1 point, stable, change <1 point ; worsening, increase≥1 point.
e) Pediatric Outcomes Data Collection Instrument (PODCI) improvement, increase ≥10 points ; stable, change <10 points ; worsening, decrease ≥10 points.

f) Short-Form-36 Physical Component Score (SF-36 PCS) improvement, increase ≥10 points; stable, change <10 points ; worsening, decrease ≥10 points.
g) Patient Inventory Questionnaire (PIQ) Breathing improvement, at least a little better; stable, no change ; worsening, at least a little worse. *T25FW, patient did not perform the test at 48 weeks because of pain after previous tests.

Safety and Tolerability

The safety analysis population includes all patients who received at least 1 dose of elosulfase alfa during the study. The most frequently reported drug-related AEs were headache (40.0% of patients), nausea, pyrexia, and vomiting (20.0% each). The nature of AEs was generally consistent with other studies in Morquio A patients (Hendriksz et al., 2014b, Burton et al., 2015). Overall, 1.7% of infusions were interrupted or discontinued due to an AE in MOR-006 versus 1.3% in the phase 3 MOR-004 study (Hendriksz et al., 2014b).

Conclusion

The MOR-006 study demonstrates that treatment with elosulfase alfa has an acceptable safety profile, even in severely disabled MPSIVA patients, and suggests the potential for beneficial effects in these patients. Most patients experienced improvement in at least one of the domains assessed. However, lack of validated tools, issues with test execution, small sample sizes, irreversibility of some symptoms, and clinical heterogeneity among patients hampered interpretability of outcomes across the study.

The study authors suggest that these results indicate that severely disabled MPS IVA patients should be assessed on an individual basis to determine the impact of treatment.

MOR-007: clinical trial in children under 5 years

Please refer to Table 21 for a reminder a study design and methodology and to Table 22 for patient baseline characteristics.

Efficacy Results

Table 55 presents the secondary objective results for MOR-007 (jones et al., 2015). In summary, the efficacy analysis showed a substantial decrease in mean normalized uKS levels within 2 weeks of treatment with elosulfase alfa, with the decreased levels being maintained over 52 weeks. The observed decline in uKS of 43.5% was comparable to that reported for older children and adult patients in the elosulfase alfa phase III studies.

Table 55. MOR-007 key results for secondary objectives

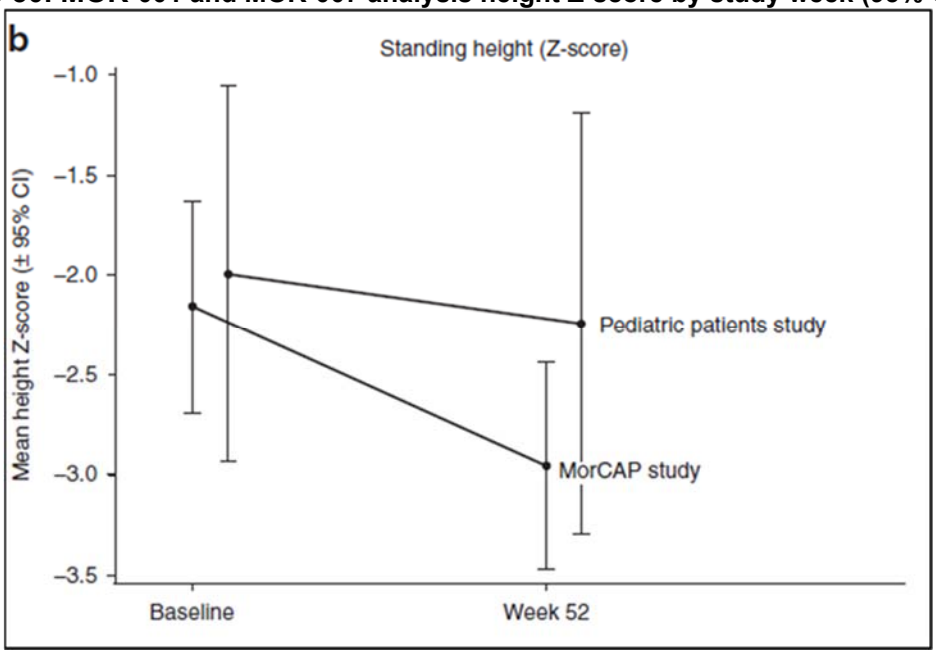
Category	Results
N in study	15
Mean (±SD) duration of exposure to elosulfase alfa	51.9 (±0.18) weeks, ranging from 51.6 – 52.1 weeks.
Mean (±SD) weekly dose received	1.9 (±0.08) mg/kg/week
Mean (±SD) percent change from baseline in urine KS	30.2% (±12.68; n=15) at 2 weeks 39.9% (±24.03; n=15) at 26 weeks 43.5% (±22.15; n=10) at 52 weeks
Mean (±SD) height	Increased 5.3 (± 2.35) cm from baseline to week 52; a mean (±SD) percent change of 5.9% (±2.53).
Mean (±SD) weight	Increased 1.7 (± 0.81) kg from baseline to week 52; a mean (±SD) percent change of 13.8% (±7.33).
Mean (±SD) height z-scores for the 12 patients, ≥2 yrs of age at baseline as compared to 25 untreated patients of similar age from MOR001	-2.0 (±1.5) (baseline) -2.3 (±1.4) (matched population to MOR-001) After 52 weeks, the treated MOR007 patients' mean (±SD) height z-score was -2.2 (±1.7) as compared to -3.1 (±1.4) in the aged matched MOR001 untreated cohort. The untreated cohort's mean (±SD) height z-score obtained after 104 weeks was -3.9 (±1.6) demonstrating a mean change of -1.6 (±1.0) over this time period.

Furthermore, treatment with elosulfase alfa resulted in an increase in the mean weight (all patients) by 1.7 (±0.8) kg from baseline to week 52; a mean percent change of 13.8% (±7.3). The mean height in patients ≥2 y of age (N = 12) increased by 5.3 (±2.4) cm from baseline to week 52; a mean percent change of 5.9% (±2.5). In patients <2 y (N = 3), the mean length increased by

6.0 (±2.7) cm from baseline to week 52; a mean percent change of 6.8% (±3.3). For all 15 patients, the mean height/length for age z-score was −1.6 (±1.6) at baseline and −1.9 (±1.6) after 52wk of treatment, the mean change from baseline at 52wk was −0.4 (±0.5).

Comparison of the current data with longitudinal growth data from the MorCAP study suggests that elosulfase alfa improves growth rates (Figure 50). The mean height z-score for the 12 patients in MOR-007 ≥2 y of age at baseline was −2.0 (±1.5), as compared to −2.2 (±1.3) in 24 untreated patients of similar age from the MorCAP study. After 52wk, height z-scores in both groups were −2.2 (±1.7) and −3.0 (±1.2), respectively. This finding is consistent with that of the phase III study where results suggested improved growth with treatment in individuals still growing (females <15 y and males <18 y).

Figure 50. MOR-001 and MOR-007 analysis height Z-score by study week (95% CI)



Conclusion

The improvement in growth (as evidenced by an increase in average height and weight) from the MOR-007 study is particularly important in MPS IVA patients. 63% of deaths in MPS IVA patients are attributable to compromised pulmonary function (Lavery and Hendriksz, 2015). MPS IVA patients have

normal-sized organs which, because of their attenuated growth and short stature, are housed within a confined space. Improvements in growth can, therefore, be associated with improved pulmonary function and endurance in these patients. Early intervention with elosulfase alfa may help to ameliorate the impact of this disorder on growth. The safety profile of elosulfase alfa observed in this younger population was similar to that observed in older children and adults (Hendriksz et al., 2014b), suggesting a favourable benefit/risk profile and has been consistently observed across the clinical studies.

MOR-008: dose comparator trial (pilot study)

The MOR-008 study (Burton et al., 2015) was excluded in the systematic literature review since it is a pilot study (see description of study design, methodology, and patient characteristics in section 9.4). However, a full description of the results is presented in this section.

CPET data showed improvements in exercise capability over 52 weeks. Maximal exercise capacity numerically increased after 25 weeks of elosulfase alfa treatment and remained relatively stable thereafter up to week 52. The greatest increases were seen in the tidal volume at peak workload and in the VO2 at VT, indicating that patients were able to breathe more efficiently and to exercise to a higher workload before reaching their VT. Of note, the VO2 at VT is not dependent on patient effort indicating that the changes seen in the CPET variables reflected physiological improvement. The VO2 at VT continued to increase beyond 25 weeks (week 25, +9%; week 52, +18%) indicating progressive improvement in exercise capacity throughout the study period.

Analysis of the remaining CPET parameters provided additional objective support that the increase in exercise capacity is not attributable to volitional factors. At baseline, mean peak RER was >1 indicating that patients exercised to a workload beyond VT, in accordance with adequate patient effort at study entry. While this does not preclude small test-to-test differences in volitional effort between patients, the peak RER remained unchanged on

subsequent CPET evaluations at weeks 25 and 52, indicating that patient performance did not change during the study. Moreover, patients showed minimal differences in peak heart rate and respiratory rate between baseline and week 52 (which remained below age-adjusted norms), indicating that exercise was terminated at similar cardiorespiratory stress levels at each study visit. These results illustrate how CPET provides an assessment of exercise capacity that is more comprehensive than the 6MWT and 3MSCT.

Despite the improvements observed in CPET measures of exercise capacity and work efficiency, improvements in endurance measures were small. These findings suggest that patients continued to self-regulate their performance to a similar degree on the volitional tests despite improvement in maximal exercise capacity. Alternatively, the relatively good endurance of the study population at baseline left little room for further improvement in the 6MWT or 3MSCT, particularly given the orthopedic abnormalities in these patients (50% with knee deformity, 40% with joint pain, and 27% with hip dysplasia at baseline) (Burton et al., 2015). Because of this ceiling effect, the 6MWT and 3MSCT test may be less suitable to assess treatment effects in patients with relatively good baseline endurance.

In addition, Treadwell et al (2017) reported a reduction in pain severity, the number of painful joints, and the words used to describe pain from the Adolescent and Pediatric Pain Tool (APPT) over the 52-week period (Treadwell et al., 2017).

Conclusion

The 52-week CPET outcomes of the MOR-008 pilot study provide evidence for a positive effect of elosulfase alfa on exercise capacity and efficiency of oxygen utilization that was not attributable to changes in either cardiac or respiratory function and pain, important factor affecting the QoL of the patients. As orthopedic challenges may limit the impact of treatment on endurance test results in these patients, analysis of data obtained during CPET may be a valuable addition to the 6MWT and 3MSCT to monitor treatment effects on cardiorespiratory capacity. No new or unexpected safety

signals, including IARs and hypersensitivity AEs, were observed. Drug generally safe and well tolerated at both doses. No death, no AE leading to withdrawal.

Real-world evidence from the MAA and MARS

Recent real-world evidence from the MAA and from the MARS registry study confirmed results from the pivotal trial (MOR-004/005) and demonstrated that, in the broad majority of the population, elosulfase alfa stabilised patients' outcomes in quality of life, ADL, and wheelchair status, and that endurance (measured by the 6MWT) remained stable in most patients (with some declining slightly with progression of the disease).

The latest MAA analysis based on [redacted] data-cut (from BioMarin data on file) and including [redacted] patients with available assessments, shows results in [redacted] patients with MPS IVA who were initiated on treatment since 2015 and [redacted] patients who were previously enrolled in the elosulfase alfa clinical trial programme ([redacted] in MOR-002, and [redacted] in MOR-004, MOR-007 or MOR-008). [redacted].

The newly initiated patients had the following improvements in:

- Endurance: mean (SD) 6MWT distance was [redacted] ([redacted]) m at baseline and increased by [redacted] m ([redacted]%) to [redacted] ([redacted]) m at last follow-up (n=[redacted]; mean treatment duration [redacted] years) (BioMarin MAA data on file). Baseline and/or follow-up data were not available for the remaining 11 patients at the time of the latest data-cut in November 2019;

- Pulmonary function: FVC and FEV1 were stable or numerically improved. In the age group of patients below 18 years old at baseline (mean treatment duration [redacted] years), percent change from baseline to the last follow-up was [redacted] ([redacted]) for FVC and [redacted] ([redacted])

for FEV1. In the age group of patients who were 18 years old or older (mean treatment duration [redacted] years), percent change from baseline to the last follow-up was [redacted]% ([redacted]L) for FVC and [redacted]% ([redacted]L) for FEV1 (BioMarin MAA data on file);

- Cardiac function: All 69 patients who had ejection fraction measured at baseline had normal findings, and left ventricular ejection fraction (LVEF) remained within the normal range during the MAA (BioMarin MAA data on file);

- Reduction in uKS levels that were comparable to those seen in the clinical trials. Mean uKS decreased rapidly and remained stable over time thereafter; mean (SD) uKS was [redacted] ([redacted]) µg/mg creatinine at baseline and decreased to [redacted] ([redacted]) µg/mg creatinine at last follow-up in treatment-naïve patients (n =[redacted]; mean treatment duration [redacted] years) (BioMarin MAA data on file). Likewise, baseline and/or follow-up data were not available for the remaining 11 patients at the time of the latest data-cut in November 2019.

A substantial portion (n=[redacted] out of a total of [redacted] patients in the MAA) of patients in the MAA started treatment prior the MAA (i.e., in clinical trials), some of whom were in the original dose-finding trial for elosulfase alfa (n=[redacted]) and therefore have been on treatment for about 10 years. These patients showed a maintenance of their endurance on average, and improvements in their lung function, indicating the durability of treatment (Mukherjee et al., 2019a, Mukherjee et al., 2020).

In addition, the real-world data collected in the Morquio A Registry Study (MARS) demonstrated the positive outcomes of elosulfalse alfa treatment in a broader population and confirmed the durability of the benefit in the long-term (Mitchell et al., 2020).

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse

events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

Elosulfase alfa is the only pharmacological treatment licensed for MPS IVA in the UK or in any other country. It is the first and only therapy that treats the underlying cause, counteracts the progress of the disease and improves the quality of life and functional status in MPS IVA patients of all ages.

The efficacy and safety of elosulfase alfa has been demonstrated in an extensive clinical programme, which was the largest and most comprehensive study programme for any LSD prior to market authorisation. Along with this comprehensive body of clinical trial evidence presented above, real-world data has been collected over five years in the MAA in England and MARS (see sections 9.6.1.2.1 and 9.6.1.2.2) and have shown consistent results with the trials; the overall results demonstrate that short-term and long-term treatment with elosulfase alfa is well tolerated, can be used in all groups of patients with a confirmed diagnosis of MPS IVA, and provides sustained benefit across a number of clinical, quality of life, and activities of daily living measures.

Clinical trials performed with elosulfase alfa assessed the impact of treatment on the systemic manifestations of MPS IVA in various domains including endurance, respiratory function, growth velocity, and mobility, as well as urine KS (Vimizim® SPC 2014). The efficacy of intravenous elosulfase alfa was evaluated in a randomised, double-blind, placebo-controlled, multinational, phase 3 (MOR-004). As noted previously, the duration of MOR-004 was limited to 24 weeks for ethical reasons, so as not to unduly prolong patient access to surgery, which was an exclusion criterion for the study.

MPS IVA patients treated with elosulfase alfa in the pivotal MOR-004 study at a dose of 2.0 mg/kg/weekly for 24 weeks experienced a statistically significant and clinically relevant improvement of the 6MWT which was a priori selected as the primary endpoint, compared to placebo (Hendriksz et al., 2014b). The primary endpoint was discussed during the CHMP protocol assistance and it

was agreed that no other single endpoint would be more sensitive to clinically relevant changes over a timeframe of 24 weeks (CHMP, 2014).

Patients also experienced numerical improvements showing a trend in favour of elosulfase alfa treatment across a majority of the secondary and tertiary endpoints, including improved performance in endurance tests (6MWT and 3MSCT), respiratory function tests (FVC, MVV, FEV1, FIVC), anthropometric measurements (standing height, length, sitting height, and weight), reducing urinary KS levels (which is a pharmacodynamic marker for biological disease activity) the performance of a number of activities of daily living, and growth (Hendriksz et al., 2014c). These improvements were consistent across all patient groups.

The CHMP noted that:

“The mean difference with placebo in the primary endpoint 6-MWT was 22.5 metres at week 24 and this was statistically significant. The clinical relevance of this difference can be derived from the secondary parameters and additional information on clinically important events. Given the improvement in 3MSCT, MVV, wheelchair dependency, orthopaedic surgery and ADL function, the observed effect of the 6MWT can be considered clinically relevant. The reduction in urine KS observed for both dosing regimens suggests a reduction in overall accumulated body and tissue storage of KS and indicates an activity of the enzyme on a lysosomal level.” (CHMP, 2014).

Longer-term data from the phase 3 extension study (MOR-005) showed that elosulfase alfa treatment for a period of 72 weeks resulted in a continuous improvement in endurance and pulmonary function, a reduction in wheelchair dependency and a reduction or deferral of surgical interventions. Interim results from the paediatric study (MOR-007) demonstrate that treatment with elosulfase alfa led to a substantial and sustained decrease in mean normalised urine KS in children <5 years of age which was comparable to that seen in MOR-004 in older children and adults. Compared to an age-matched cohort of untreated children from MOR-001, children treated with elosulfase

alfa in the MOR-007 study demonstrated a trend for favourable effects on growth.

Recent evidence from the MAA confirmed the results from the pivotal trial and its extension (MOR-004/005) and demonstrated that, in the broad majority of the population, elosulfase alfa stabilised patients' outcomes in quality of life, ADL, and wheelchair status, and that endurance (measured by the 6MWT) remained stable in most patients (with some declining slightly with progression of the disease).

For patients who were initiated to treatment in the MAA programme, results showed a rapid decrease and a subsequent stabilisation over the long-term in uKS, as well as initial improvements in endurance and pulmonary function and then stabilisation in these measures in the long-term. In addition, data showed that patients were not progressive in their dependency on a wheelchair and that their quality of life, pain, and ability to perform activities of daily life improved upon treatment initiation and remained stable in the long-term.

A number of patients (n=[redacted] out of [redacted] patients) in the MAA were in the original dose-finding trial MOR-002/100 for elosulfase alfa and therefore have been on treatment for about 10 years. These patients showed a maintenance of their quality of life, endurance for most of them, as well as improvements in their lung function, indicating the durability of treatment (see section 9.6.1.2.1).

Overall, the presented data provide further evidence that long-term treatment with elosulfase alfa has a positive impact on patients' quality of life and ability to perform activities of daily living and stabilises or slows down the progression of the disease.

When compared to projected natural history data, treatment with elosulfase alfa has demonstrated meaningful improvements to all groups of patients with a confirmed diagnosis of MPS IVA, particularly given the unrelenting progressive nature of the disease, the heterogeneity of disease manifestations, broad age ranges studied, and the chronic effects caused by years of damage due to accumulated GAGs. In the long-term these improvements could likely translate into reduced mortality - as observed in 10

years MPS VI (a related condition) where ERT-treated patients had reduced mortality compared to untreated patients (16.5% vs.50.0%) (Giugliani et al., 2014) – improved cardiopulmonary function a reduced disease progression.

There is a strong correlation between endurance, pulmonary function measures and height with patient-reported outcomes, which suggest that increases in height and endurance/mobility and pulmonary function measures may be robust surrogate parameters of, and are accompanied by, gains in health-related quality of life in patients with MPS IVA (Lampe et al., 2015).

The safety profile of elosulfase alfa is in line with the safety profiles for other ERTs. The most common side effects seen in the clinical development programme were infusion related reactions, which were generally mild to moderate, and the frequency was higher during the first 12 weeks of treatment and tended to decrease with time. The reactions were manageable by infusion rate adjustments. No new safety concerns were identified in the real-world setting, both in MARS (Burton et al., 2020b, PSUR, 2019) and in the MAA (BioMarin MAA data on file, 2019).

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Table 56. Limitations and strengths of the clinical evidence base

Limitations	Strengths
Short duration of the pivotal MOR-004 study and a primary endpoint of the 6MWT • MOR-004 was limited in duration to 24 weeks for ethical considerations, because patients were not allowed to undergo surgery during the study. • MOR-004 therefore comprised only a short duration placebo arm.	• The CHMP accepted that the 6MWT endpoint was the outcome most sensitive to change over a 24-week period. • The CHMP concluded that the design of study MOR-004 and the inclusion and exclusion criteria were acceptable. The chosen study objectives, comparator and sample sizes were all considered adequate, and the selected endpoints were

	considered suitable for the objectives of the MOR-004 study. • Randomisation strategy and blinding were appropriate, and the statistical methods were acceptable and in line with the 2012 CHMP protocol assistance (CHMP, 2014).
The placebo arm of MOR-004 involved enhanced care and so was not representative of the usual standard of care	**The MOR-001 (MorCAP) study provides long-term longitudinal data on the natural history of disease in the relevant patient cohort.** • A comparison of the MOR-004/005 120-week data with the natural history from MorCAP/MOR-001 represents the best available current evidence on long-term outcomes.
The HRQoL data collected in the Phase 3 study was limited • Data was collected on the MPS HAQ	**The published burden of illness study evaluated quality of life and other self-reported outcomes for both patients and caregivers** • A broader set of quality of life data was collected in patients treated with elosulfase alfa in England during the period of the MAA (as reported in the item **Error! Reference source not found.**). • Long-term results from HRQoL from the final analysis of MOR-005 demonstrate improvement in quality of life in key domains of MPS-HAQ (**Error! Reference source not found.**) • There is a strong correlation between some clinical outcomes (specifically, endurance, pulmonary function and height) and patient-reported outcomes thus indicating that improvements in these outcomes would

	translate into meaningful benefits to patients in terms of improved quality of life (Lampe et al., 2015). The MAA results support this finding (as reported in section **Error! Reference source not found.**)
	Size and breadth of the clinical dataset • The Biomarin-sponsored studies comprise the largest dataset ever of patients with MPS IVA and represent the most comprehensive evidence base for any LSD therapy prior to launch. • The CHMP noted that the MOR-004 study population was large relative to other Phase 3 studies for other ERTs (CHMP, 2014). • Biomarin continue to evaluate the real-world effectiveness of elosulfase alfa within the global data registry MARS (as described in the section **Error! Reference source not found.**) and other local initiatives around the globe, such as the collection of clinical outcomes in the English patients during the period of the MAA. • The efficacy and safety of elosulfase alfa has been assessed across a wide range of endpoints and multiple domains. • No association was found between TAb or NAb positivity and decreases in normalized uKS. No association was found between drug exposure and occurrence of Grade 2 treatment-emergent AEs, hypersensitivity AEs, or with TAb or NAb titers

	• In the pivotal Phase 3 study (MOR-004), results on the primary endpoint of the 6MWT were statistically significant for the group receiving elosulfase alfa weekly. In the same study, both treatment regimens (weekly and qow) reduced urine KS compared to placebo (a secondary endpoint), and the results were statistically significant. The results for other endpoints, although not significant, were numerically superior, and tended to favour elosulfase alfa over placebo. • The results from MOR-005 indicate that the clinical benefits seen in MOR-004 are continued or sustained over a period of 120 weeks (Hendriksz et al., 2016c). • The results observed in the clinical trial setting are confirmed by the clinical outcomes collected from the real-world use of elosulfase alfa in patients treated in England
	Results of the clinical programme are expected to be generalisable to the population of MPS IVA patients in England • Taken together, the participants in the MOR-004/005 and MOR-007 (paediatric patients <5 years) studies, including from UK sites, are representative of the total MPS IVA patient population and so the results are generalisable to the patient population in England. • Additionally, as agreed in the MAA, during the period of the agreement a broader set of clinical outcomes were collected.

	• The CHMP noted that: "The combination of study population in the elosulfase alfa clinical development programme appears to encompass the spectrum of age and disease severity of the overall patient population diagnosed with Morquio A syndrome. More specifically, the inclusion of patients based on genetic typing as conducted in the MOR-004 trial, results in an attenuated population which is more comparable with the population expected to be treated. Disease characteristics appear representative of the range of disease symptoms reported in the literature and are similar to characteristics of MPS IVA patients in the natural history study MorCAP (MOR-001). Since study MorCAP represented approximately 10% of the overall patient population, results from the elosulfase alfa clinical studies are anticipated to be generalizable to the overall MPS IVA population" (CHMP, 2014) • Patients diagnosed with MPS IVA and initiated to elosulfase alfa in the MAA programme showed a rapid improvement in quality of life, ADL, endurance, pulmonary function, and then stabilisation of these measures in the long-term. A number of patients (n=[redacted] out of [redacted] patients analysed) in the MAA were in the original dose-finding trial for elosulfase alfa and therefore have been on treatment for about 10 years. These patients showed a maintenance of their endurance on average, and improvements in their lung

	function, indicating the durability of treatment.
Challenges and limitations of observational studies • Lack of consistency in data collection and missing data; • Lack of randomisation and control group, leading to challenges in comparative analysis and potential risks of bias; • In MAA/MARS, patients could receive surgical interventions (vs in clinical trials), which can impact outcomes; • Surgeries were not captured in the MAA; • Lack of data on compliance rates (e.g. in MARS) which could impact outcomes • Broader perspective and causation between outcomes (confounding factor) are missing, given that not all outcomes are captured.	**Long-term, real-world data collected over 5 years in the MAA and MARS are consistent with clinical trial results** • MAA data (and partly MARS) reflect the real-world population and clinical practice in England • MAA and MARS captured data in a bigger sample size of patients with MPS IVA who are treated with elosulfase alfa, and therefore provide a more comprehensive dataset; • Longer follow-up of treated patients compared to RCTs; real-world, long-term results have shown to be consistent with those from the clinical trials.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

- The elosulfase alfa clinical development programme spans patients of all ages and with disease characteristics representative of nature of the disease, and so is representative of the total patient population. UK sites and UK patients have been included in the programme.
- A wide range of clinical endpoints have been evaluated, as well as the outcomes which are important to patients, the burden on caregivers and families and HRQoL. Moreover, the relationship

between clinical outcomes and PRO have also been evaluated (Lampe et al., 2015) in 24 German patients.

- A broader set of QoL outcomes were collected in the MAA, MARS, and from other real-world evidence from different countries and are described in section **Error! Reference source not found.**. The observed results reinforce the findings of the trial program and demonstrate durability of treatment in clinical outcomes, patient-reported outcomes and ADL.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

BioMarin is not aware of any such factors. In fact, as pointed out in section 8.9.2 above, the CHMP noted that the study participants in the pivotal Phase 3 study, MOR-004, were expected to b representative of the population of MPS IVA patients most likely to be treated with elosulfase alfa (CHMP, 2014).

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable.

As evidence from MAA a wide variety of patients can benefit from the treatment with elosulfase alfa. As discussed in the previous committee discussions there are no a priori criteria to define patient who will benefit most from the treatment.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

The combination of respiratory dysfunction, cardiovascular complications, short stature, and musculoskeletal impairments, results in increased levels of pain and fatigue, and a progressive loss of endurance and functional capacity in MPS IVA patients (Hendriksz et al., 2013a, Hendriksz et al., 2014c). Due to the severity of the skeletal manifestations, the non-skeletal manifestations are frequently overlooked when considering management options despite their significant contribution to disease progression and significant impact on quality of life (QoL) (Hendriksz et al., 2014c). These include loss of endurance, increase in pain and fatigue and the psychological impact (Hendriksz, 2014) of the disease.

Loss of endurance and wheelchair dependency

The progressive loss of endurance, the increase in pain, and the fatigue lead to increased dependence on wheelchair use, as patients lose the ability to undertake normal daily activities such as washing, making the bed and pouring a drink. The MorCAP study shows that 41% of the patients cannot cut their nails, 31% cannot tie their shoelaces, 22% cannot iron their shirts and 22% cannot open a jar (Harmatz et al., 2013). General endurance and stair climbing in particular are greatly impaired because of a combination of muscle weakness and reduced endurance. Reduced endurance in MPS IVA patients leads to greater use of and dependence upon a wheelchair. Quality of life significantly deteriorates with wheelchair dependency (Hendriksz et al., 2014c).

In a study on burden of illness in which patients reported the outcomes themselves, the burden of disease of MPS IVA was investigated in adults (≥ 18 years, n=27) and children (7-17 years, n=36). It related among other things to the impact on mobility, quality of life, pain and fatigue (Hendriksz et al., 2014c).

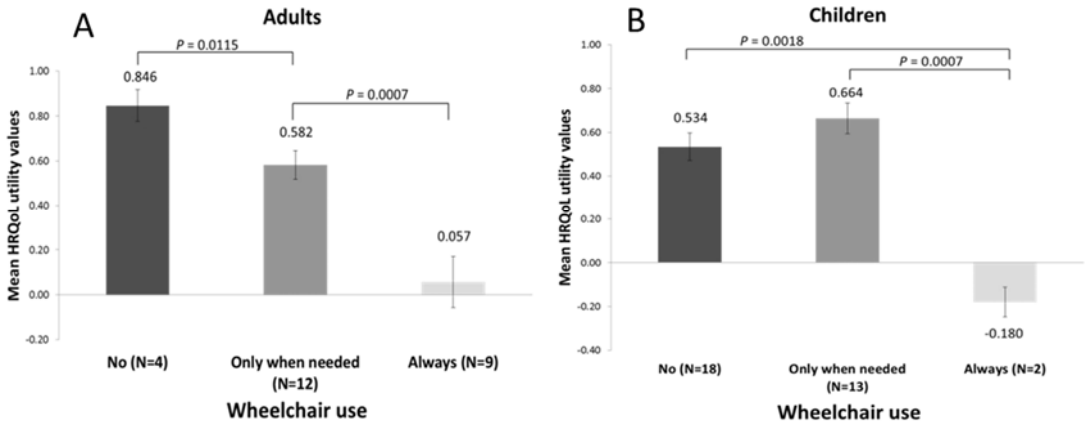
The study used the Euro-QoL (EQ)-5D-5L questionnaire which is a generic standardised measure of health status developed by the EuroQoL group and applicable to a wide range of health conditions and therapies. It comprises five dimensions (5D): mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The study also included questions from the mobility domain and caregiver domain of the MPS Health Assessment Questionnaire (MPS HAQ).

Results showed that QoL of MPS IVA patients is most related to the ability to remain independently mobile without becoming wheelchair dependent. Their QoL reduces dramatically if patients always have to use their wheelchair. Even a slightly better mobility (wheelchair use only when needed) greatly improves QoL. Maintenance of functional capacity and mobility paired with better pain management are likely to improve QoL (Hendriksz et al., 2014c).

MPS IVA patients have quality of life limitations in daily living caused by low endurance and impaired mobility (Hendriksz et al., 2013a). Respiratory and cardiovascular impairments play a significant role, alongside classic musculoskeletal abnormalities, in reducing strength and endurance. Low endurance pushes patients towards a greater reliance on walk aids and wheelchairs, which has been shown to directly impact quality of life (

Figure 51). As noted in section 9.9.1 above, there is a strong correlation between endurance, pulmonary function measures and height with patient-reported outcomes, which suggest that increases in height and endurance/mobility and pulmonary function measures may be robust surrogate parameters of, and are very likely be accompanied by, gains in health-related quality of life in patients with MPS IVA (Lampe et al., 2015).

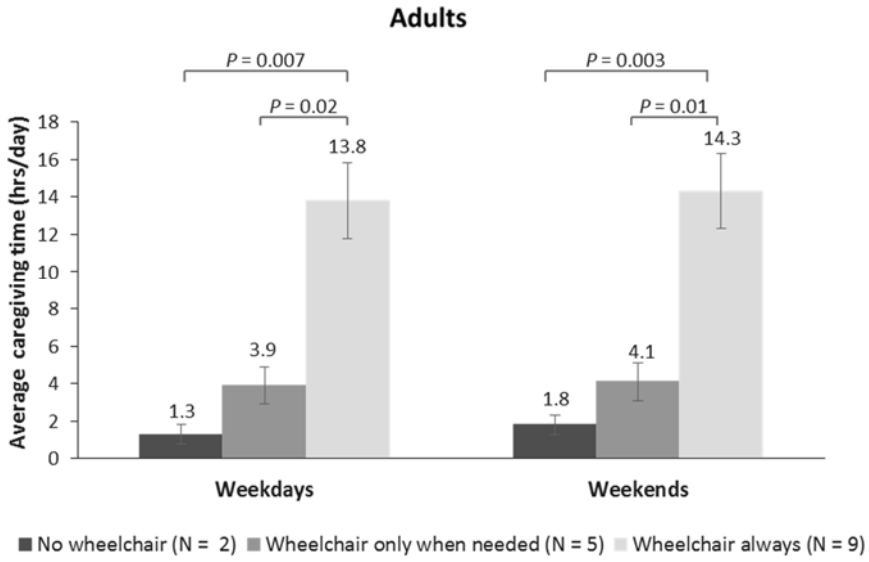
Figure 51. Relationship Between Reliance on a Wheelchair and Quality of Life (Hendriksz 2014c)



HRQoL scores for adults (A) and children (B). The EQ-5D-5L is a validated tool for measuring patient quality of life. 1.00 = patient perception of perfect health; 0.00 = patient perception of death; negative values indicate that the patient feels worse than death. The higher level of quality of life shown in child patients who sometimes use a wheelchair may be related to a decrease of pain and increase in activity that a wheelchair may provide (Hendriksz et al., 2013a).

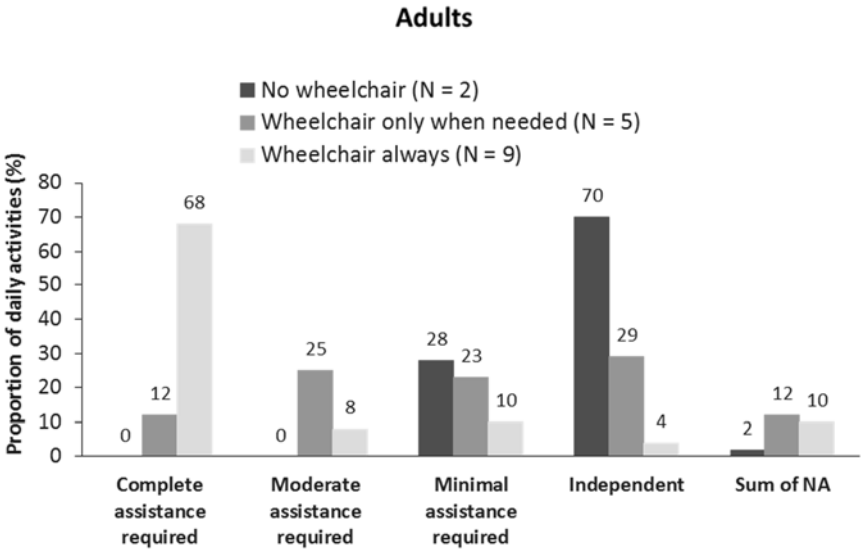
As decreased endurance and progressively worsening pain cause patients to lose independence, the caregiver burden significantly increases. Increases in wheelchair use lead to a significant increase in the level of support and number of hours requires of caregivers (Figure 52 and Figure 53), also supporting the limited independence patients have when being more compromised for endurance or mobility (Hendriksz et al., 2014c).

Figure 52. Relationship between Reliance on a Wheelchair and time burden for Caregivers



Source: Hendriksz 2014d

Figure 53. Relationship between reliance on a wheelchair and requirement for assistance



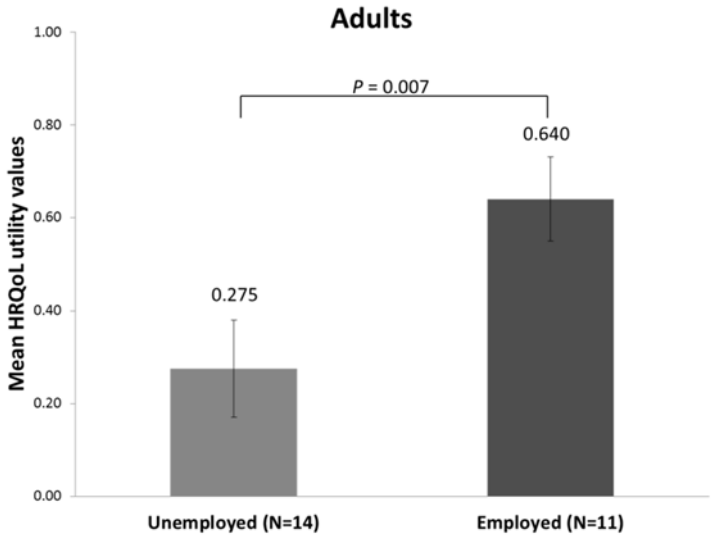
Source: Hendriksz 2014d

Psychological impact

Patients who maintained mobility and endurance are most often working. As patients become more reliant on a wheelchair, fewer patients are in work to the point where only 22% of patients who are always in a wheelchair are working.

This is an important impact since patients with MPS IVA have a normal IQ and intelligence, both of which are unaffected by their disease. Patients who report that they are out of work have a significantly lower quality of life (Figure 54) (Hendriksz et al., 2013a). If patients can maintain greater endurance and mobility, the results from burden of illness study indicate they retain greater independence, ability to work, less carer burden and a high quality of life.

Figure 54. Relationship Between Ability to Work and Quality of Life



Source: Hendriksz 2013a

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

As noted in section 10.1.1 above, MPS IVA is a progressive condition, so the patient's health related QoL deteriorates as disease progresses and patient gets older.

As has already been noted, patients with MPS IVA show a progressive decline in endurance. This reduced endurance leads to wheelchair dependency. QoL significantly deteriorates with wheelchair dependency, while the requirement for caregiver assistance increases.

HRQoL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment

on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The only HRQoL tool used in the clinical study was the MPS HAQ which, as described in the clinical study results, was found to be sensitive in two domains, the caregiver domain and the mobility domain. As described above the self-care domain was considered less relevant by patients.

For relevance to this evaluation the most relevant measure was regarding use of a wheelchair in Q33.3 of the MPS HAQ mobility domain, which patients reported via the questionnaire after each clinical evaluation, children were reporting this with assistance from their carer. Wheelchair shift results are presented in Table 57. Relevant changes in use of a wheelchair take time to develop and, as such, this data is taken from the MOR-005 extension study (week-72 interim analysis).

This analysis is relevant as burden of illness studies which were undertaken to better understand patient reported outcomes showed significant changes in HRQoL with wheelchair status.

Moreover, new evidence related to the impact of elosulfase alfa treatment on the HRQoL of patients with MPS IVA has been published in the last years, further testifying the benefit and positive impact of the treatment (Mukherjee et al., 2019a).

Following is a list of the HRQoL results from the clinical programme and also from real-world studies described in this document (Table 57).

Table 57. Table summarizing the locations of HRQoL results in the submission document

Study	QoL/PRO Instruments	Location in the document
MOR-005	MPS HAQ	Section 9.6.1.1
MAA	MPS HAQ EQ-5D-5L BPI APPT	Section 9.6.1.2.1
MARS	EQ-5D-5L	Section 9.6.1.2.1

Additional to the mentioned above, the MPS society published a poster during the SSIEM congress in 2018 describing the testimonies of patients treated with elosulfase alfa in England during the MAA, as described subsequently:

Patient Reported Outcomes in MPS IVA Patients Receiving Enzyme Replacement Therapy: The Patient Reported Experience after the First Two Years on an English Managed Access Agreement

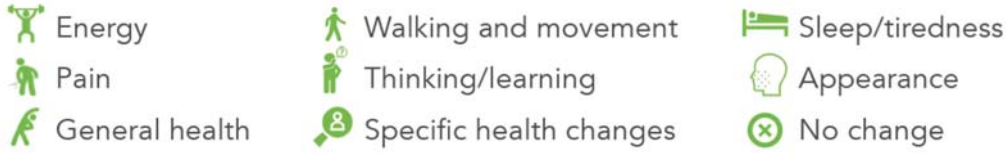
Methods

Patients who had not received elosulfase alfa before MAA (aka. ERT-naïve patients) were asked at 4, 8 and 12 months on treatment under the MAA if they had noticed any changes since starting treatment. At 24 months, ERT-naïve patients were asked if they had noticed any changes in the last year.

Patients who previously received elosulfase alfa as part of a clinical trial were asked at 12 and 24 months after joining the MAA if they had noticed any changes in the last year.

Changes were reported by either the patient of their parent/caregiver in cases of patients under 18 years old. The changes reported by patients were grouped under as list in Figure 55.

Figure 55. Patient testimonies report groups



Results

Of the 56 patients who had completed at least 4 months on the MAA, 42 consented to their testimonies being shared; a total of 99 testimonies were reported. Patients were aged between 1-58 years when they joined the MAA; mean age was 29.5 years.

Twenty-two patients were elosulfase alfa naïve on entering the MAA; 20 patients had previously received elosulfase alfa as part of a clinical trial. Not all patients joined the MAA at the same time or provided a testimony at each applicable time point varying the number of responders in each period.

After 12 months on the MAA

At 12 months, 19 testimonies were collected from naïve patients with 95 reported changes. The most commonly reported changes in naïve patients affected their general health (24/95, 25%), energy levels (19/95, 20%) and sleep/tiredness (16/95, 17%) (

Table 58).

An additional 20 testimonies were collected from patients previously receiving elosulfase alfa as part of a clinical trial with 53 reported changes. The most commonly reported changes in this group affected their energy levels (11/53, 21%), general health (10/53, 19%) and specific health benefits and walking and movement (both 7/53, 13%) (Table 58).

Table 58. Reported changes in ERT-naïve patients and patients previously receiving elosulfase alfa as part of a clinical trial after 12 months on the MAA

Naïve patients		Elosulfase alfa trial patients	
% of reported changes N=95	Specific changes reported	% of reported changes N=53	Specific changes reported
Energy (20%)	Increased energy (n=12), more stamina (n=3), everyday activities easier (n=1), ability to do more in a day (n=1), more active (n=1), physically active (n=1)	Energy (21%)	Increased energy (n=4), more stamina (n=2), no deterioration in energy levels (n=2), no deterioration in stamina (n=1), able to do more in the day (n=1), more active (n=1)
Walking and movement (14%)	Walking easier/more (n=5), easier movement (n=2), hands/wrists stronger (n=1), can manage steps (n=1), more toned (n=1), able to transfer from/to wheelchair better (n=1), able to stand longer without legs trembling (n=1), fine motor skills – no change, builds lego (n=1)	Walking and movement (13%)	Walking easier/more (n=3), no deterioration in physical ability/mobility (n=2), movement a lot better (n=1), feeling stronger (n=1), more toned (n=1)
Sleep/tiredness (17%)	Less tired (n=9), better sleep (n=4), felt better upon waking (n=3)	Sleep/tiredness (8%)	Less tired (n=2), better sleep (n=2)
Pain (6%)	Less pain (n=4), no pain (n=1), increased pain (n=1)	Pain (6%)	No pain (n=1), not waking in night with pain (n=1), back hurting more (n=1)
Thinking/learning (6%)	More engaged (n=3), more clarity of thought (n=1), better concentration (n=1), better handwriting (n=1)	Thinking/learning (9%)	More clarity of thought (n=1), better concentration (n=1), more engaged (n=1), behaviour improved (n=1), better handwriting (n=1)
Appearance (1%)	Better skin complexion (n=1)	Appearance (2%)	Skin better (n=1)
General health (25%)	Growth (n=4), weight gain (n=3), weight not changed much (n=1), happier in themselves (n=3), not as ill (n=2), better appetite (n=2), better social skills (n=2), missing less school (n=1), speech clearer and louder (n=1), ability to lose weight (n=1), more confidence (n=1), improved quality of life (n=1), more relaxed (n=1), improved mood (n=1)	General health (19%)	More independence (n=3), not as ill (n=2), happier in themselves (n=2), weight gain (n=1), ability to lose weight (n=1), generally well (n=1)
Specific health changes (9%)	Breathing better (n=3), lungs clearer (n=1), eyesight better (n=1), wears glasses now (n=1) better sense of smell (n=1), reduced number of ear infections (n=1), hearing improved, grommets fitted (n=1)	Specific health changes (13%)	Breathing better (n=2), less diarrhoea (n=1), lungs clearer (n=1), eyesight better (n=1), no recent chest infections (n=1), hearing slightly improved (n=1)
No change (1%)	No change/nothing to report (n=1)	No change (9%)	No change/nothing to report (n=5)

After 24 months on the MAA

At 24 months, 6 testimonies were collected from naïve patients with 19 reported changes. The most commonly reported changes in naïve patients affected their energy levels (4/19, 21%), walking and movement, sleep/tiredness, thinking/learning and general health (all 3/19, 16%) (Table 59).

An additional 19 testimonies were collected from patients previously receiving elosulfase alfa as part of a clinical trial with 46 reported changes. The most commonly reported changes in this group affected their genera health and walking and movement (both 9/46, 20%) (Table 59).

Table 59. Reported changes in naïve patients and patients previously receiving elosulfase alfa as part of a clinical trial after 24 months on the MAA

Naïve patients		Elosulfase alfa trial patients	
% of reported changes N=19	Specific changes reported	% of reported changes N=46	Specific changes reported
Energy (21%)	Increased energy (n=2), more stamina (n=1), physically active (n=1)	Energy (13%)	Increased energy (n=3), more stamina (n=1), able to do more in the day (n=1), physically active (n=1)
Walking and movement (16%)	Walking easier/more (n=2), easier movement (n=1)	Walking and movement (20%)	Poor mobility (n=2), worsened posture (n=2), walking easier/more (n=1), continuing to get about [walking] (n=1), better grip (n=1), no deterioration in physical ability (n=1), posture is good (n=1)
Sleep/tiredness (16%)	Less tired (n=2), better sleep (n=1)	Sleep/tiredness (13%)	Feeling tired (n=2), less tired (n=2), better sleep (n=1), ability to manage tiredness better (n=1)
Pain (5%)	Increased pain (n=1)	Pain (7%)	Increased pain (n=2), little pain (n=1)
Thinking/learning (16%)	Better concentration (n=1), increased vocabulary (n=1), more engaged (n=1)	Thinking/learning (9%)	Better concentration (n=1), mental age improvement (n=1), started writing (n=1), following instructions (n=1)
Appearance	–	Appearance	–
General health (16%)	Better appetite (n=1), improved quality of life (n=1), more relaxed (n=1)	General health (20%)	Generally well (n=4), quality of life improved (n=3), growth (n=1), happier in themselves (n=1)
Specific health changes (11%)	Fewer headaches (n=1), eyesight better (n=1)	Specific health changes (9%)	Coughing/wheezing (asthma) worsened (n=1), corneal clouding improved (n=1), no recent chest infections (n=1), periods started again (n=1)
No change	–	No change (11%)	No change/nothing to report (n=2), no deterioration – on treatment since 2012 (n=1), stable since started treatment (n=1), remained stable, been on treatment 6 years (n=1)

Conclusions

During the first two years of the elosulfase alfa MAA, naïve patients most frequently reported changes in their energy levels and general health. For patients who had previously received elosulfase alfa as part of a clinical trial, the most common areas of change reported during the MAA were walking and movement and general health.

The changes reported here reflect the overall patients' experience over a two-year period on the MAA and therefore may not be attributable solely to treatment with elosulfase alfa:

- Some of the changes experienced in the younger patients may constitute a developmental effect e.g. improved handwriting or increased vocabulary
- Other treatments or surgeries may have contributed to the changes reported

It should be noted that under the terms of the MAA, elosulfase alfa treatment may be stopped if patients do not meet set criteria for continuation of treatment, although the testimonies presented here are not part of the criteria

to remain on the MAA, concerns over access to treatment may affect the information that patients are willing to share in their testimonies.

This study highlights a range of outcomes that are important to patients' lives that may not be collected via current standard PRO tools. These findings may act as a guide to the selection of suitable tools or the development of disease specific measures for use in future studies.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

During the period of the MAA the EQ-5D-5L instrument was used to assess HRQoL of patients treated with elosulfase alfa. Results are available in the section **Error! Reference source not found.**.

HRQoL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

Appendix 3, Section 17.3.4 details the systematic searches performed to identify relevant utility and MPS HAQ data. The search strategies are provided within this appendix.

A utilities SR was conducted. The methods were documented in a protocol (MPSIVA_SRs_Protocol_v1.1_20191008.docx) in line with PRISMA-P requirements (Moher et al., 2015).

The research questions were as follows:

Utilities

- What Health State Utility Values (HSUVs) (utilities, disutilities, utility decrements or increments) are available for patient or caregiver health in MPS IVA?
- What MPS HAQ data are available in MPS IVA?
- What caregiver utilities (EQ-5D in particular) are available for caregivers to patients with MS?
- Which of these are most suitable for use in the NICE HST evaluation of ESA in MPS IVA? 'Suitablity' is assessed by, 1) whether the utility derivation method meets the preferences of NICE, 2) whether the population enrolled in the utility study matches well the patients enrolled in ESA clinical trials and 3) how robust the utility estimate is. Suitability is also assessed by considering the relevance of the HSUVs to the health states (HSs) in the model.

We ran a separate search in November 2020 to assess if any new articles had been published since the last SR, which was conducted in November 2019. The search terms and inclusion/ exclusion criteria were the same as the original search of November 2019. The new search generated 20 articles at the 1st pass (EMBASE/ MEDLINE), and 8 articles after the 2nd pass, which are reported separately from the main SR report (see Table 63). Three of these articles (Giordano et al., 2016, Opara et al., 2012, Hendriksz et al., 2015a) were already included in the SR and therefore not reported in the list of new articles below.

For the utilities SR, key sources included: Embase, Medline, Medline in Process/epublications ahead of print, National Health Service Economic Evaluation Database (NHS EED) and Health Technology Assessment Database (HTAD) (Centre for Reviews and Dissemination, University of York

(CRD)), last 2 years (yrs) of International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International and European conferences (2018/2019), SR/CUA reference lists, included trials reference lists, any supplemental Google search to identify full texts of abstracts identified in electronic searching, EuroQoL-5 dimensions (EQ-5D) website, the University of Sheffield's School of Health and Related Research Health Utilities (ScharrHUD) database, and Health Technology Assessment (HTA) websites (NICE, Scottish Medicines Consortium (SMC), Haute Autorité de Santé (HAS), All Wales Medicines Strategy Group (AWMSG), Canadian Agency for Drugs and Technologies in Health (CADTH)).

The search strings use Emtree Medical Subject Heading (MeSH) terms and broad free-text terms, using a specific method developed and recommended by Wichor Bramer[3], a biomedical information specialist in Erasmus MC, Rotterdam, to create high-quality and thorough searches in Embase.com (Embase and Medline together).

The population terms are bespoke and include a comprehensive set of free text terms and the index term for morquio syndrome.

The utilities filter is adapted from the published filter of Arber et al. (Arber et al., 2015; Arber et al., 2017). The electronic database searches cover all terms from the published filter (FSF2). Additional terms are also included, based on Arber et al. 2015, encompassing all preference-based measures (PBMs) (rather than just EQ-5D terms). The filter, therefore, incorporates EQ-5D, Time Trade-Off (TTO) or Standard Gamble (SG), other types of PBM (HUI, AQoL, QWB, 15D, SF-6D), SF-36 and SF-12. In addition, child-specific utility data were sought, including EQ-5D-Y, child health utility (CHU-9D), adolescent health utility measure (AHUM), 16D and 17D.

The utilities filter was combined with MPS IVA terms, or with caregiver AND MS terms. Further, MPS HAQ terms were combined with MPA IVA terms.

Utilities were unlimited by date.

[3] http://www.slideshare.net/wichor

The complete search strings are reported in Appendix 3, Section 17.3.4.

The inclusion and exclusion criteria used to select studies from the literature are given in Table 60 and Table 61 below:

Table 60. Inclusion criteria used for utilities studies

Characteristic	Inclusion criteria
Population	MPS IVA (Morquio syndrome) for patient or caregiver outcomes Multiple sclerosis for caregiver outcomes
Mixed populations +	For mixed populations, at least 80% must be the population of interest *or* subgroup data for the population of interest must be reported separately Mixed data examples include mixed MPS disease data and mixed adult/child populations
Interventions/ comparators	No restrictions, or none
Outcomes	HSUVs, disutilities or increments/decrements for relevant health states++ Individual (patient or caregiver) derived mean or median health state utilities from indirect generic HRQoL measure (EQ-5D-3L or -5L index values), or direct valuation by TTO or SG General public valuations of vignettes using TTO or SG Disutilities or decrements for AEs associated with treatments for MPS IVA MPS-HAQ
Study design	Any (HSUVs may be estimated from a range of different study designs) SRs* or CUAs #
Date limits	No restrictions
Country limits	No restrictions
Child abstract	Linked abstracts with unique data will be retained
Publication type	Original articles or errata TA documents, if original source not available elsewhere
Languages	Electronic searching will not be limited by English language Any non-English language articles deemed relevant will be discussed with BioMarin to decide on final inclusion. For non-English language articles that are included, Vendor will utilise existing BioMarin support to translate and/or extract relevant information from included articles (if needed §)

Abbreviations: AE, Adverse Event; CUA, cost-utility analysis; EQ-5D, Euroqol 5-Dimensions; HRQoL, Health Related Quality of Life; HSUV, health-state utility value; SG, Standard Gamble; SR, Systematic Review; TA, technology appraisal; TTO, Time Trade-Off; UK, United Kingdom

+ 80% will be used as an initial standard, though arbitrary, cut-off, for mixed populations. During screening, dependent upon the data identified, the 80% cut-off may be revised, and the rationale documented.

++ HSs of relevance include (but are not limited to) stable disease, wheelchair (various degrees of use thereof), paraplegia, assisted/supported ventilation, AE states

* SRs will be kept in at 1st pass for cross-referencing/bibliography checking purposes (flagged in Endnote) but will be excluded at 2nd pass.

CUAs that are themselves the original source of (otherwise unpublished) utility data will be included. CUAs using utilities the original source of which is published elsewhere will be kept in at 1st pass for cross-referencing/bibliography checking purposes (flagged in Endnote) but will themselves be excluded at 2nd pass.

§ Vendor language capabilities include English, Czech, Danish, French, German, Hungarian, Italian, Polish, Portuguese and Spanish. If an article is outside of these languages but suspected to be relevant

the article will be discussed with BioMarin. If no resolution is possible (no linguist available) the article will be listed in the report for transparency as an article for which eligibility could not be ascertained.

Table 61. Exclusion criteria used for utilities studies

Characteristic	Exclusion code & criterion	Explanatory notes
Publication type	e1 pub: Publication type not of interest	e.g. letters, commentaries, editorials, notes, press/news articles, protocol-only articles.
Duplicate	e1 dup: Duplicate/copy	Exact duplicates or copy abstracts, for example where the content is almost identical. If there are discrepancies in the actual data reported, then both will be retained, and the discrepancy noted
Child abstract	e1/e2 child: Child abstract or sub-study with no unique data	To be determined at 1st or 2nd pass stage
Languages	e2 lang: Non-English language article agreed between BioMarin and Vendor to be ineligible	Non-English language articles deemed potentially relevant will be discussed with BioMarin to decide on final inclusion.
Population	e1/e2 pop: Animal data Healthy volunteers Not MPS IVA Not MPS IVA or multiple sclerosis (for caregiver data)	Multiple sclerosis is considered a proxy disease
Mixed populations	e1/e2 mix: Mixed population enrolled e.g. mixed MPS disease populations	<80% of the enrolled patients are the population of interest and subset results are not reported separately for the population of interest
Interventions / comparators	No restrictions or none	
Study design	e1/e2 design:	
	Non-systematic reviews	Non-systematic reviews or non-comprehensive SRs will be excluded
	SRs/MAs	Relevant SRs and MAs are kept in at 1st pass for cross-referencing/bibliography screening purposes but will be excluded after 2nd pass, except if MA data not available elsewhere
	Pilot studies	Not robust enough evidence for use
	CUAs, CEAs	Relevant CUAs are kept in at 1st pass for cross-referencing purposes but will be excluded after 2nd pass (unless the CUA is the only source of the, otherwise unpublished, utility). The original papers for the utilities reported in the CUA will be sought for inclusion
	Case reports	
	PK/PD study only	
	In vitro studies	Human in vivo only

Characteristic	Exclusion code & criterion	Explanatory notes
	Other	Validation studies Lectures AB only SLRs or CUAs (as bibliography cannot be checked)
Outcomes	e1/e2 out: No outcome of interest +	Studies not reporting utility values or MPS-HAQ or ADL Studies reporting HRQoL condition-specific data, except for MPS-HAQ or ADL Utilities not relating to specific health states of interest Utilities valued by experts or HCPs rather than by patients General public valuations of vignettes using TTO, SG EQ-5D-VAS data AB only articles without any actual data reported No numeric data reported Registry records with no results available Mapping algorithms
Mapped utilities	e2 mapped utility	
Non-EQ-5D utilities	e2 other PBM	SF-6D, HUI2, HUI3, AQoL, QWB, 15-D, 16-D, 17-D, MAUI, CHU9D, AHUM data will be excluded at second pass under this separate code, for listing in the report separately.
Date limits	No restrictions	
Country limits	No restrictions	

Abbreviations: 1st, first; 2nd, second; AB, abstract; AHUM, adult health utility measure; AQoL, Assessment of Quality of Life; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; e1, excluded on abstract screening; e2, excluded on full paper screening; HCP, health care provider; HRQoL, health-related quality-of-life; HUI, Health Utility Index; MA, meta-analysis; MAUI, Multi-Attribute Utility Index; MPS IVA, Mucopolysaccharidosis type IVA; MS, multiple sclerosis; PBM, preference-based measure; PD, Pharmacodynamic; PK, Pharmacokinetic; QWB, Quality of Well-Being; SF-6D, short form 6 dimensions; SR, Systematic Review
+ Outcomes of interest are EQ-5D, TTO, SG, MPS-HAQ and ADL

The electronic database searches identified 272 citations (235 from Medline/Embase, 0 from Medline InProcess/e-publications, 35 from Cochrane Central Register of Controlled Trials (CENTRAL) and 2 from Cochrane Database of Systematic Reviews (CDSR)). After duplicate removal in Endnote (14 citations), and after first pass (title/abstract) screening (211 exclusions, see Appendix 3 Table 142), 47 papers were screened at second pass. Following full paper review (21 exclusions, see Appendix 3 Table 143), 26 articles were included from electronic sources. A further 10 articles were

identified via hand-searching. A total of 36 citations were, therefore, included in the SR (Table 62).

Table 62: Summary listing of included studies (n=36)

Author, Year	Title
(Acaster et al., 2013)	A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis
(Ali and Cagle, 2014)	Psychological health in adults with morquio syndrome
(Bassi et al., 2014)	The coexistence of well- and ill-being in persons with multiple sclerosis, their caregivers and health professionals
(Benito-León et al., 2011)	The CAREQOL-MS was a useful instrument to measure caregiver quality of life in multiple sclerosis
(Buhse et al., 2015)	Caregivers of older persons with multiple sclerosis: determinants of health-related quality of life
(Cooper et al., 2015)	Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA: A Highly Specialised Technology Evaluation. Southampton Health Technology Assessments Centre (SHTAC)
(Forbes et al., 2007)	Informal carer activities, carer burden and health status in multiple sclerosis
(Gani et al., 2008)	Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK
(Giordano et al., 2012)	Health-related quality of life and depressive symptoms in significant others of people with multiple sclerosis: A community study
(Giordano et al., 2016)	Low quality of life and psychological wellbeing contrast with moderate perceived burden in carers of people with severe multiple sclerosis
(Gupta et al., 2012)	Self-reported burden among caregivers of patients with multiple sclerosis
(Harmatz et al., 2013)	The Morquio A Clinical Assessment Program: Baseline results illustrating progressive, multisystemic clinical impairments in Morquio A patients
(Hendriksz et al., 2014b)	Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study

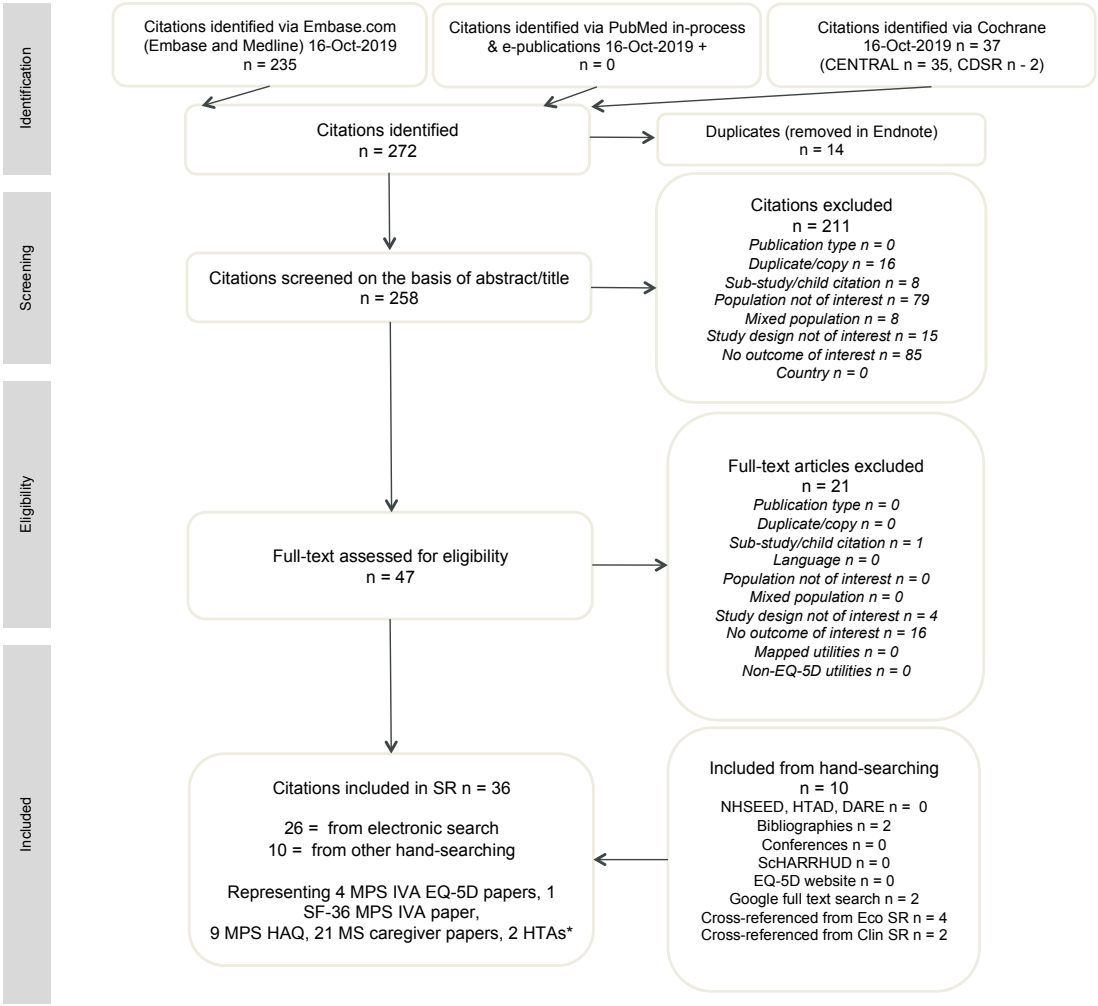
Author, Year	Title
(Hendriksz et al., 2014c)	Burden of disease in patients with Morquio A syndrome: Results from an international patient-reported outcomes survey
(Hendriksz et al., 2014a)	Burden of disease suffered by patients with Morquio syndrome type A: Results from a patient-reported outcomes survey
(Hendriksz et al., 2014c)	The Burden Endured by Caregivers of Patients With Morquio A Syndrome: Results From an International Patient-Reported Outcomes Survey
(Hendriksz et al., 2015b)	Multi-domain impact of elosulfase alfa in Morquio A syndrome in the pivotal phase III trial
(Hendriksz et al., 2018b)	Impact of long-term elosulfase alfa on activities of daily living in patients with Morquio A syndrome in an open-label, multi-center, phase 3 extension study
(Hughes et al., 2017)	Clinical outcomes in a subpopulation of adults with Morquio A syndrome: results from a long-term extension study of elosulfase alfa
(Joshi et al., 2015)	Determinants of health utility among caregivers of individuals with multiple sclerosis (MS)
(Joshi et al., 2016a)	A comparison of EQ-5D-3l and SF-6D among caregivers of individuals with multiple sclerosis
(Joshi et al., 2016b)	Psychometric properties of the Euroqol-5-dimensions questionnaire (EQ-5D-3L) among multiple sclerosis caregivers
(Lampe et al., 2014)	Burden of disease suffered by caregivers of patients with Morquio syndrome type A: Results from a self-reported outcomes survey
(Lampe et al., 2015)	Relationship between patient-reported outcomes and clinical outcomes in patients with morquio a syndrome
(Lavery et al., 2017)	Impact of elosulfase alfa treatment on patient-reported outcomes in morquio a syndrome: Results from the first year of an english managed access agreement
(Patti et al., 2007)	Caregiver quality of life in multiple sclerosis: A multicentre Italian study
(Perrin et al., 2015)	A Disproportionate Burden of Care: Gender Differences in Mental Health, Health-Related Quality of Life, and Social Support in Mexican Multiple Sclerosis Caregivers

Author, Year	Title
(Peters et al., 2013)	Carer quality of life and experiences of health services: A cross-sectional survey across three neurological conditions
(Petrikis et al., 2019)	Quality of life and emotional strain in caregivers of patients with multiple sclerosis
(Phillips et al., 2011)	The Hidden Toll of Caregiver Burden in Multiple Sclerosis [Poster]
(Rivera-Navarro et al., 2009)	Burden and health-related quality of life of Spanish caregivers of persons with multiple sclerosis
(SMC, 2015)	Elosulfase alfa, 1mg/mL concentrate for solution for infusion (Vimizim®) SMC No. (1072/15)
(Solari et al., 2006)	A longitudinal survey of self-assessed health trends in a community cohort of people with multiple sclerosis and their significant others
(Soto, 2017)	Evaluation and impact on the quality of life of patients with mucopolysaccharidosis IV-a (Morquio a) at the Colombian Southwestern
(Stewart et al., 2011)	The hidden toll of caregiver burden in multiple sclerosis
(Wittenberg and Prosser, 2013)	Disutility of illness for caregivers and families: A systematic review of the literature

Abbreviations: CAREQOL-MS, caregiver quality of life in multiple sclerosis; EQ-5D, EuroQol 5-dimensions; MS, multiple sclerosis; NICE, National Institute of Health and Care Excellence; SF-6D, short form 6-dimensions; SHTAC, Southampton Health Technology Assessments Centre; SMC, Scottish Medicines Consortium; UK, United Kingdom

The screening process is summarised in a PRISMA flow diagram (Figure 56).

Figure 56.PRISMA Flow-chart for study identification and selection of utilities data



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; Clin, clinical; DARE, Database of Abstracts of Reviews of Effects; Eco, economic; EQ-5D, EuroQoL-5 dimensions; HAQ, Health Assessment Questionnaire; HTA, Health Technology Assessment; MPS, Mucopolysaccharidosis; MS, Multiple Sclerosis; SR, systematic review
+Search run 16-Oct-2019 and e-alert set up and tracked until 13-Nov-2019
*Lavery et al. 2017 reported both EQ-5D and MPS HAQ, hence total apparently being 36

Table 63. List of new relevant published studies (November 2020)

Author, Year	Title
(Bray et al., 2020)	Preference-based measures of health-related quality of life in congenital mobility impairment: a systematic review of validity and responsiveness
(Hughes et al., 2019b)	Elosulfase alfa treatment on patient-reported outcomes for Morquio A: Results from a Managed Access Agreement in England
(Mitchell et al., 2019b)	Clinical characteristics of French-Canadians with Morquio A syndrome
(Moisan et al., 2020)	Clinical characteristics of patients from Quebec, Canada, with Morquio A syndrome: A longitudinal observational study
(Pennington, 2020)	Inclusion of Carer Health-Related Quality of Life in National Institute for Health and Care Excellence Appraisals

10.1.6 Provide details of the studies in which HRQL is measured. Include the following but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

MPS IVA data

The health states (HSs) relevant to the model included the following: Asymptomatic, No wheelchair use, Sometimes use wheelchair, Wheelchair-dependent, Paraplegic, Pre-death/End-stage and Death.

Hendriksz et al. 2014c reported EQ-5D-5L (UK TTO tariff) in 27 adult and 36 children with MPS IVA, and its linked AB was retained as it reported the standard error (SE). Of the adult p, 52% were between the ages of 18 and 24 years, 85% lived with their parents and 7.4% lived alone (Hendriksz et al., 2014c). Of the child patients, these were reported as being in the age range 7-17 in Hendriksz et al. 2014 (Hendriksz et al., 2014c) and 5-17 years in Hendriksz et al. 2014. Lampe et al. 2014 (Lampe et al., 2014) reported EQ-5D-5L in 24 MPS IVA patients in Germany. A summary of utilities identified is given in Table 65.

The latest MAA results were not captured in the SLR because they are not published. However, the full results are provided in section 9.6.1.2.1.

Utilities used in previous submissions (NICE, SMC, CADTH) from Economic SR

The adult data from Hendriksz et al. 2014c were used to inform the HSUVs in the previous NICE (NICE, 2015a, NICE, 2015b, NICE, 2015c) and SMC (SMC, 2015) submissions for the No wheelchair use (0.846), sometimes use a wheelchair (0.582) and wheelchair dependent (0.057) HSs. The asymptomatic HSUV was 1.00, based on standard UK population EQ-5D scores for children aged 0-9 yrs. End-stage disease HSUV was reported from the NICE submission as 0.024, and a utility increment for every 10m gain in 6MWT for ESA pts of 0.02 (corresponding to a utility increment of 0.11 for No wheelchair use and Sometimes wheelchair use HS for pts on ESA, due to the improvement with ESA of 55.7m in 6MWT). A utility increment of 0.017 was applied to the paraplegic and wheelchair-dependent HSs, corresponding to a 0.0885 litre improvement in Forced Vital Capacity (FVC): the source was not identified in the NICE submission, although the Evidence Review Group (ERG) noted that this could have been academic-in-confidence (AIC) data

from Lampe et al. 2014. A further utility benefit was reported in the submission of 0.02, for pts receiving their weekly ESA infusions at home. Utility decrements for recovery from surgery were based on UK expert clinical opinion from a Delphi panel: muskuloskeletal surgery (cervical fusion surgery, spinal decompression, etc) 0.250 decrement; other surgery (e.g. tonsillectomy, corneal replacement) 0.005 decrement (Cooper et al., 2015).

In the CADTH submission (CADTH, 2016a, CADTH, 2016b), the pre-death HSUV was from a subset of the wheelchair-dependent patients who had ventilation support in the PRO study.

Multiple Sclerosis (as proxy disease) caregiver data overview

Twenty-one citations (18 studies) reported MS caregiver data (Bassi et al., 2014, Adang et al., 2020, Buhse et al., 2015, Benito-León et al., 2011, Forbes et al., 2007, Giordano et al., 2016, Giordano et al., 2012, Joshi et al., 2016a, Joshi et al., 2016b, Joshi et al., 2015, Patti et al., 2007, Perrin et al., 2015, Peters et al., 2013, Rivera-Navarro et al., 2009, Stewart et al., 2011, Wittenberg and Prosser, 2013, Acaster et al., 2013, Gupta et al., 2012, Phillips et al., 2011, Solari et al., 2006)

Linked citations included those of Joshi et al. (Joshi et al., 2016a, Joshi et al., 2016b, Joshi et al., 2015), and Phillips et al. 2011 provided the poster to the Stewart et al. 2011 abstract.

Only two studies reported EQ-5D, however: Acaster et al. 2013, and Joshi et al. (Joshi et al., 2016a, Joshi et al., 2016b, Joshi et al., 2015), the latter study and Phillips et al. 2011 reported SF-6D.

Ten papers reported SF-36 only (Bassi et al., 2014, Rivera-Navarro et al., 2009, Benito-León et al., 2011, Forbes et al., 2007, Giordano et al., 2012, Giordano et al., 2016, Patti et al., 2007, Perrin et al., 2015, Petrikis et al., 2019, Solari et al., 2006) and, of these, only Giordano et al. 2012 reported SF-36 in caregivers according to the MS patient's Expanded Disability Status Scale (EDSS) level. Two of these reported EDSS score as a significant predictor of caregiver SF-36 scores (Patti et al., 2007, Rivera-Navarro et al.,

2009). A significant association between EDSS and caregiver fatigue status was shown in Petrikis et al. 2019 with fatigue status separately shown also to be significantly associated with SF-36.

SF-12 only was reported by Buhse et al. 2015 and Peters et al. 2013. SF-12 and SF-6D were reported by two further papers, Gupta et al. 2012 and Phillips et al. 2011.

A disutility for being a caregiver to an MS patient (0.14) was reported in Wittenberg et al. 2013, but the derivation method was not described. Wittenberg et al. 2013 referenced Argyriou et al. 2011b as the source, but on examination of this latter reference the disutility itself was not reported.

Gani et al. 2008 estimated disutilities by EDSS HS, from an assumed maximum disutility of 0.14 (from Alzheimer's disease) according to the amount of caregiver time required for pts in each HS. The resulting disutilities per patient were: 0.00, 0.00, 0.00, 0.01, 0.01, 0.02, 0.03, 0.05, 0.11, 0.14 for EDSS scores 0.0, 1.0, 1.5-2.0, 2.5-3.0, 3.5-4.0, 4.5-5.0, 5.5-6.0, 6.5-7.0, 7.5-8.0, 8.5-9.5, respectively. In the previous ESA NICE submission, caregiver utilities were similiarly based on hours of caregiving (these coming from Hendriksz et al. 2014) and the data from Gani et al. 2008.

MS (as proxy disease) caregiver EQ-5D

Acaster et al. 2013 reported that EQ-5D (UK TTO tariff, range -0.59 to 1.0) in 200 caregivers of MS patients (caregiver mean age 50.88, mean EQ-5D 0.74, SD 0.28) was significantly lower (p=0.003) than in 200 matched[4] controls (mean age 50.99, mean EQ-5D 0.82, SD 0.25) in a UK cross-sectional study. Response rates were 75% (200/266) for caregivers to MS patients (pts) and 95% (200/211) in controls. SF-36v2 was also measured. The Patient Determined Disease Steps Scale (PDDS), which has been mapped to EDSS (Kurtzke, 1983), was used to assess mobility in the MS patient. PDDS ranges from 0 (normal) to 8 (bedridden)[5]. EQ-5D disutilities (standard error (SE)) of

[4] Matched on age, sex, employment status and habitation status

[5] 0 normal, 1 mild disability, 2 moderate disability, 3 gait disability, 4 early cane, 5 late cane, 6 bilateral support, 7 wheelchair/scooter, 8 bedridden

caregiving relative to the control population by PDDS status (0-1, 2-3, 4, 5, 6, 7, 8) were -0.002 (0.053), -0.045 (0.057), -0.142 (0.062), -0.160 (0.055), -0.173 (0.054), -0.030 (0.038), -0.095 (0.075), respectively. The utilities in caregivers at PDDS 4, 5 and 6 were significantly lower than in controls (p value NR but interval of 1.96xSE showing significance plotted in Fig. 2 of article).

Joshi et al. (Joshi et al., 2015; 2016a; 2016b) reported significant differences between EQ-5D-3L and SF-6D in MS caregivers in a US cross-sectional survey (recruited via the registry North American Research Committee on MS (NARCOMS)). Mean (SD) values were 0.83 (0.17) for EQ-5D (range -0.04, 1.00) and 0.74 (0.14), range 0.345 to 1.00 for SF-6D (Joshi et al., 2016a). By comparison, EQ-5D in the general population was 0.91 (Joshi et al., 2015). Male caregivers had lower EQ-5D than males in the general population (0.83 and 0.88, respectively) (Joshi et al., 2015). Significant predictors of differences between the two measures included caregiver marital status, family annual income and the patient's disability status. Patient disability status had a negative effect on caregiver utility via its (negative) impact on subjective caregiver burden (Joshi et al., 2015). Ceiling effects were observed for EQ-5D-5L (with at least 15% of respondents reporting the best HS), but floor effects were absent (Joshi et al., 2016b).

MPS HAQ data

MPS HAQ was reported in 9 citations (Harmatz et al., 2013, Hendriksz et al., 2015a, Hendriksz et al., 2018b, Hughes et al., 2017, Lavery et al., 2017, Lampe et al., 2015, Soto, 2017, Hendriksz et al., 2014c, Hendriksz et al., 2014b).

MorCAP baseline (BL) MPS HAQ item-level data were reported in Harmatz et al. 2013b, but not at the domain level.

Hendriksz, Lavery et al. 2014d reported on an international survey (Brazil (BRA), Columbia (COL), DEU, ESP, Turkey (TUR)). Again, the domain-level MPS HAQ was NR but the %s of patients requiring assistance with specific ADL, as measured by MPS HAQ, were reported (in Fig. 3a (adults) and 3b

(children) of the FPA Hendriksz, Lavery et al. 2014d further paper reporting %s of pts having different levels of difficulty with particular tasks but no domain-level data was Soto, 2017, providing data from 28 MPS IVA patients in Columbia. The authors comment that the greatest difference from the healthy population was in the domains of pain/discomfort and mobility, and that pt HRQoL was most affected by self-care problems, wheelchair use and usual activities.

Lavery et al. 2017 reported the mean change in caregiver assistance domain for 35 pts receiving ESA in England, under the MAA, was -0.86 (SD 9.10) after 1 yr of data collection to March 2017. The authors indicated that from the patient-reported outcomes (PROs) collected, the data supported continuing treatment in 33/35 pts, with the majority reaching or exceeding the benefit level required by the MAA.

Hughes et al. 2017 reported the improvement between BL and 120 wks in mean scores for the 3 MPS HAQ domains self-care, mobility and caregiver assistance in 37 adult patients from MOR-005. At BL the mean (SD) domain scores in the ITT population were 2.7 (2.2), 5.4 (2.7) and 23.0 (10.0), respectively. By 120 wks (n=33), the corresponding least squares (LS) mean changes from BL (SE) were -0.43 (0.2), -0.76 (0.24) and -1.02 (0.9). In a sub-population of pts (excluding those who had had orthopaedic surgery or were non-compliant with the study protocol (had missed ≥20% of scheduled infusions)), the LS mean changes from BL were more pronounced: at BL (n=22) the mean (SD) domain scores in the sub-population were 2.0 (1.9), 5.5 (2.5) and 23.7 (10.5), for the self-care, mobility and caregiver assistance domains, respectively. By 120 wks (n=30), the corresponding least squares (LS) mean changes from BL (SE) were -0.58 (0.2), -0.81 (NR) and -1.24 (NR). By comparison, in the MorCAP population (10 pts on no treatment for 2 yrs), with BL values of 2.4 (1.9), 5.4 (2.4) and 25.8 (2.4), after 2 yrs, the self-care domain score worsened, with LS mean change (SE) of 0.53 (0.3). Mobility and caregiver assistance domain LS mean (SE) changes from BL were −0.20 (0.5) and 0.29 (1.3), respectively. Further follow-up data (LS mean change from BL) for MOR-005 ITT and sub-population and MorCAP studies at 1 yr

and 2 yrs are reported in Hendriksz, Parini et al. 2018b6. The data showed that MOR-005 pts had sustained significant reductions (i.e. improvements) in mobility and self-care domain LS mean scores vs. BL at 1 and 2 yrs and a trend toward a decrease in the level of caregiver-assistance required at 2 yrs. These improvements were greater in those pts treated with weekly ESA (MOR-005 including a treatment arm of ESA every other week). The follow-up data in MorCAP showed that untreated pts showed no improvement over 2 yrs, with patients worsening in two of the three domains (mobility and self-care). The earlier 24 wk data for MOR-005 were reported in Hendriksz, Guigliani et al., 2015d and Hendriksz, Burton et al., 2014b.

[6] These data are extracted in full in the Data Extraction Table, MPS HAQ tab.

Table 64. Summary of EQ-5D-5L original source data identified in MPS IVA patients

Author, year, country, type of publication	Country	Health state	Respondent	No. of participants	Mean HSUV (SD) [SE] (95% LCI, UCI)
Hendriksz, 2014 FP (Hendriksz et al., 2014b)	BRA, COL, DEU, ESP, TUR, UK	Adult - no wheelchair use	Pts	4	0.846 [0.071]
		Adult - wheelchair when needed (some use)	Pts	12	0.582 [0.063]
		Adult - always using a wheelchair (wheelchair-dependent)	Pts	9	0.057 [0.113]
		Child - no wheelchair use	Pts & Caregiver (closest)	18	0.534 [0.063]
		Child - wheelchair when needed (some use)	Pts & Caregiver (closest)	13	0.664 [0.069]
		Child - always using a wheelchair (wheelchair-dependent)	Pts & Caregiver (closest)	2	-0.180 [0.069]
Hendriksz, 2014 FP (Hendriksz et al., 2014a)	BRA, COL, DEU, ESP, TUR, UK	Employed MPS IVA Adult	Pts	11	0.640 (NR)
		Unemployed MPS IVA Adult	Pts	14	0.275 (NR)
Lavery, 2017 AB (Lavery et al., 2017)	UK	MPS IVA	Pts & Caregiver (closest)	33	NR+
Lampe, 2015 FP (Lampe et al., 2015)	DEU	MPS IVA – All patients (adult and child)	Pts & Caregiver (closest)	21	0.552 (0.342)
		MPS IVA - Adult	Pts	13	0.422 (0.363)
		MPS IVA - Child	Pts & Caregiver (closest)	8	0.763 (0.160)

Abbreviations: AB, Abstract; BRA, Brazil; COL, Columbia; DEU, Germany; ESP, Spain; FP, full paper; HSUV, health state utility value; NR, not reported; Pts, patients; SD, standard deviation; SE, standard error; TUR, Turkey; UK, United Kingdom
+ Change from baseline was reported at 52 wks: mean change in EQ-5D-5L 0.04 (SD 0.27)

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The only HRQoL results published are from the published burden of illness study published for MPS IVA (Hendriksz et al., 2014c).

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

Adverse events are predominately infusion related adverse events, which are mostly managed by slowing infusions and premedication, as such are not considered to have a substantive relevant impact on HRQoL.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Health state utility values (Table 65) were derived from an analysis of the MAA dataset, as explained below (for the clinical results see section 9.6.1.2.1):

The ERT-Naïve cohort of patients were considered for the analysis, as there was no EQ-5D collected at baseline (pre-treatment phase) the Ex-Trials patients. Ex-Trials patients had their first EQ-5D utility values collected at MAA enrolment, and the mean treatment duration of Ex-Trials patients at MAA enrolment was 5.7 years;

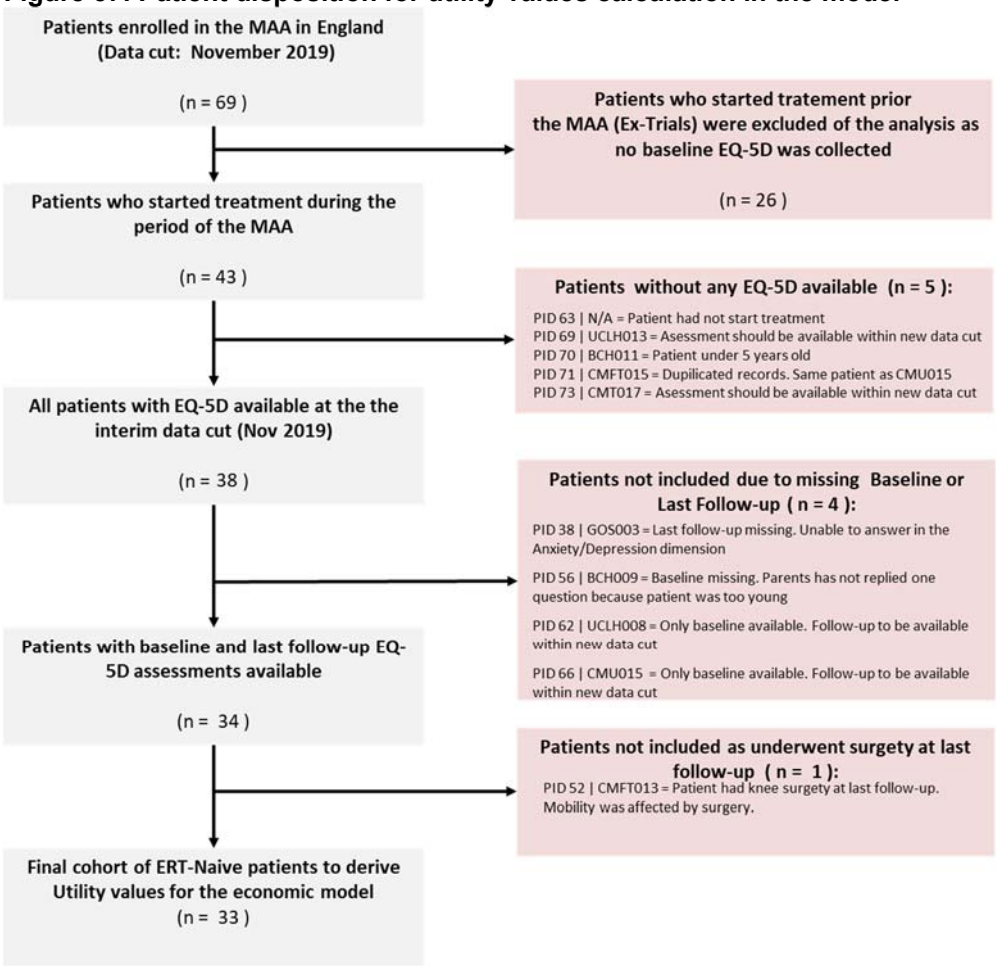
Utility values for untreated patients were derived from the baseline EQ-5D and utility values for treated patients were derived from the last assessment available (last follow-up);

Patients without baseline or any additional follow-up assessment after baseline were not considered for this calculation;

Patients who underwent surgery at last follow-up were not considered in the analysis. Patients after surgery usually recover from the event within year, which means the utility values should be restored to similar levels observed prior the surgery. In cases which the last assessment available were affected by a surgery, the patients were not included for the base case scenario.

The patient disposition for the utility calculation is provided in the Figure 57:

Figure 57: Patient disposition for utility values calculation in the model



Utility decrements for surgeries (Table 66) are derived from clinical opinion as is the period to which they are applied. Caregiver disutilities (Table 67) were taken from the published literature (Gani et al., 2008, Acaster et al., 2013) and are only used in scenario analysis.

Table 65: Health state utility values

Health state	Utility value for Untreated Patients	Utility value for patients treated with elosulfase alfa
Asymptomatic	1.000	1.000
No WC use	0.468	0.659
Sometimes uses WC	0.368	0.562
WC dependent	0.080	0.155
Paraplegic	0.057	0.166
Pre-death	0.024	0.024

Table 66: Surgery-related utility decrements and duration

	Disutility	Untreated Period (months)	Treated Period (months)
Cervical Fusion Operation	0.250	6	4
Genus Valgum surgery	0.250	6	4
Spinal decompression surgery	0.250	6	4
Hip surgery	0.250	6	4
Lower spine surgery	0.250	6	4
Aortic valve replacement	0.010	6	4
Tonsillectomy	0.005	2	1
Ear tube placement	0.005	2	1
Corneal replacement	0.005	2	1
Cataract surgery	0.005	2	1

Table 67: Caregiver-related disutility values

Health State	Gani et al 2008 (Basecase)	Acaster et al 2013
Asymptomatic	0	0
Symptomatic (No WC use)	0	0
Sometimes use WC	-0.02	-0.142
WC dependent	-0.11	-0.142
Paraplegic	-0.14	-0.142
Predeath	-0.14	-0.095

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical expert advisers assessed the applicability of HRQoL utility values through the means of an expert panel discussion and questionnaire session, in accordance with the Delphi technique. The process was conducted in December 2013.

For the existing economic model, the utility values were derived directly from the MAA dataset, so no further validation via clinical experts via Delphi technique was conducted. As some part of the Delphi panel conducted in December 2013 are still valid, the original report is provided.

Objectives of the Delphi process

The Delphi process used in health economics is a proven method in which expert opinion is sort to help provide information about certain parameter values used in a model and/or to validate certain model assumptions. Due to the limitations in some elements of data for this ultra-rare disease, the objectives of this particular Delphi panel process were to:

- Derive parameter values in the economic model, where data was absent; and

- Validate certain modelling assumptions.

Participating clinicians

The following expert clinicians took part:

- Dr Chris Hendriksz - Clinical lead- Adult Inherited Metabolic Disorders, Manchester Academic Health Science Centre, The Mark Holland Metabolic Unit, Salford Royal Foundation NHS Trust, United Kingdom
- Dr Derralyn Hughes – Senior Lecturer, Honorary Consultant, University College London, United Kingdom
- Dr Fiona Stewart - Regional Medical Genetics Unit, Belfast City Hospital. Northern Ireland. United Kingdom
- Dr Santra Saikat – Consultant, Paediatric Inherited Metabolic Disorder, Birmingham Childrens Hospital. United Kingdom
- Dr Simon Jones – Consultant - Paediatric Inherited Metabolic Disorder, Royal Manchester Children's Hospital, Manchester, United Kingdom
- Dr Tarekegn Hiwot – Consultant, Adult Inherited metabolic disorders at Queen Elizabeth Hospital, Birmingham
- Dr Maureen Cleary – Consultant, Metabolic Paediatrician, Great Ormond Street Hospital, London United Kingdom
- All the participants were clinical experts from the United Kingdom (UK) who were chosen for their experience of treating patients with MPS IVA.

Methodology

The Delphi process comprised to 2 rounds of online questionnaires, using the website *surveymonkey.com*. The first question consisted of 39 questions. 9 questions on disease progression, 12 questions on surgeries, 2 questions on mortality, 4 questions on quality of life and 12 questions on resource use and costs.

The second questionnaire was created based on the results provided from the first round. If consensus had been reached for a question in the first round, then that particular question was not asked again in the second round. If consensus was not reached in the first round the results from the first round were provided alongside the second round question which was either repeated to see if the clinicians, provided with their colleague's anonymous answers, would change their response, or if it was felt to be more appropriate the question was re-worded. Further questions were added into the second round based on some of the responses from the first-round questions. The second-round questionnaire consisted of 42 questions. There were 11 questions on disease progression, 12 questions on surgeries, 2 questions on mortality, 2 questions on quality of life and 15 questions on resource use and costs.

Following the 2 rounds of online questionnaire, clinicians met in a consensus meeting in Birmingham on 3rd December 2013. The answers given in the two questionnaires were presented and participants discussed their answers until consensus was reached.

Responses

Both questionnaires were distributed to 7 clinicians. 5 responses were received from the first questionnaire and 5 responses from the second questionnaire. However, the clinicians who responded in the first questionnaire were not necessarily the same as those that responded in the second questionnaire. Five clinicians participated in the consensus meeting.

The questions asked

The HRQoL utility values for the "Never use wheelchair (symptomatic)", "Sometimes use wheelchair" and "Always use wheelchair" states are derived from analysis on quality of life survey conducted by BioMarin. They are as follows.

- Never use wheelchair symptomatic - 0.846 *(new utilities provided in item 10.1.9)*

- Sometimes use wheelchair - 0.582 (*new utilities provided in item 10.1.9)*

- Always use wheelchair - 0.057*(new utilities provided in item 10.1.9)*

All responders agreed with the above values in the first questionnaire and so no further questions asked in 2nd round questionnaire or expert panel meeting.

The utility value for the pre death state was derived from PRO data for patients that are always in a wheelchair and require ventilation and is said to be 0.024. All responders agreed with this in Questionnaire 1 and again, no further questions were asked in 2nd round questionnaire or expert panel meeting

An analysis of a German-based MPS IVA patient-reported outcomes study showed that for every 40m improvement in 6MWT the HRQoL utility value improved by 0.08 (Lampe 2014). Therefore, it was asked “Would you expect that treatment would increase the quality of life of patients in a given health state, due to symptom relief, in addition to delaying the disease progression?” All responders answered yes in response to this question in the first questionnaire and so no further questions asked in 2nd round questionnaire or expert panel meeting.

It was asked “Would you expect MPS IVA patients with paraplegia due to surgical complications to have the same quality of life as MPS IVA patients that are in the "Always use wheelchair" state due to the progression of the disease?. In Questionnaire 1, all responders agreed that patients in these states would not have the same quality of life. However some said that they felt patients who are paraplegic would have a worse quality of life than those "Always in a wheelchair" and some felt that patients that are paraplegic would have a better quality of life than those that are in the "Always in a wheelchair" state as they will have better cognitive abilities and cardiorespiratory status. In Questionnaire 2, the question was changed to ask which state would have the worst quality of life, always or paraplegic? 80% said that quality of life of paraplegic patients would be worse than those in the always use wheelchair state and 20% said that the quality of life of the always in a wheelchair would

be worse than those who are paraplegic due to the fact that the disease has progressed more. In the expert panel meeting consensus was reached that QoL of patients that are paraplegic due to surgery complications will have a worse QoL at first but overall would be better than “always”

In the second questionnaire, the clinical advisers were asked “Would answer be different depending on whether patients move into the paraplegic state from the “Never use wheelchair state” or the "sometimes use wheelchair state"?”. 40% said Yes; 40% said No; 20% said possibly. In the expert panel meeting, this question became irrelevant as it had been previously decided that cervical fusion surgery would only happen in the sometimes use wheelchair state.

10.1.11 Please define what a patient experience in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The model health states represent the most patient relevant impacts in terms of increasing dependency on a wheelchair for assistance in endurance. As such the HRQL overs the variance as described from the literature description of the changes in a patients HRQL with increasing wheelchair dependence. For patients who are asymptomatic, normalised values of HRQL are taken as a proxy value.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The quality of life was mapped as reported in the section 10.1.9.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The quality of life was mapped as reported in the section 10.1.9.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

In a progressive disease such as MPS IVA HRQL changes with time, in the described model this changes with increasing wheelchair dependence.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

EQ5D-5L results collected during the period of the MAA were mapped following the EUROQoL recommendations to establish the relevant health utilities.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.

- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The same MAA maintenance criteria are expected to be used as continuation rules for treatment with elosulfase alfa following the end of the MAA period in December 2021. NHSE will rely on clinician reporting to assess compliance with continuation criteria.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

A PDF copy of all included studies should be provided by the sponsor.

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

An economic and cost/HCRU SR was conducted. The methods were documented in a protocol (MPSIVA_SRs_Protocol_v1.1_20191008.docx) in line with PRISMA-P requirements (Moher, 2015).

The research questions were as follows:

Economic evaluations

- What cost-utility analyses (CUA), cost-benefit analyses (CBA), cost-effectiveness analyses (CEA), cost-consequence analyses (CCA), cost-minimisation analyses (CMA) or budget impact analyses (BIA) have been conducted in MPS IVA?

Costs/HRCU

- What are the most robust direct and indirect healthcare costs associated with MPS IVA or treatments for MPS IVA (from a UK payer perspective)?
- What are the most robust indirect and societal costs relevant to the UK model (e.g. productivity losses, absenteeism, presenteeism, patient/family or caregiver costs)?
- What are the total costs associated with MPS IVA?
- What estimates of UK resource use (NHS/PSS perspective) in MPS IVA are the most robust, for the paediatric and adult populations?
- What are the main cost categories and cost drivers in patients with MPS IVA?
- What is the economic burden of MPS IVA or multiple sclerosis (as a proxy disease) on caregivers to patients with MPS IVA?

We conducted an updated search in November 2020 to assess if any new articles had been published since the last SR in November 2019. The search terms and inclusion/ exclusion criteria were the same as the original search of November 2019. The new search generated 19 articles at the 1st pass (EMBASE/ MEDLINE and 11 papers of other note), and 5 articles after the 2nd pass, which are reported separately from the main SR report.

For the economic, cost and HCRU SR, key sources included: Embase, Medline, Medline in Process/epublications ahead of print, National Health Service Economic Evaluation Database (NHS EED) and Health Technology Assessment Database (HTAD) (Centre for Reviews and Dissemination, University of York (CRD)), last 2 years (yrs) of International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International and European conferences (2018/2019), SR/CUA reference lists, included trials reference lists, any supplemental Google search to identify full texts of abstracts identified in electronic searching, CEA registry, RePEc (EconPapers), and Health Technology Assessment (HTA) websites (NICE, Scottish Medicines Consortium (SMC), Haute Autorité de Santé (HAS), All Wales Medicines Strategy Group (AWMSG), Canadian Agency for Drugs and Technologies in Health (CADTH)).

The search strings use Emtree Medical Subject Heading (MeSH) terms and broad free-text terms, using a specific method developed and recommended by Wichor Bramer[8], a biomedical information specialist in Erasmus MC, Rotterdam, to create high-quality and thorough searches in Embase.com (Embase and Medline together).

The population terms are bespoke and include a comprehensive set of free text terms and the index term for morquio syndrome.

The economic filter is adapted from the published EMBASE G filter of Glanville et al. 2009 and published as a report in collaboration with CADTH and added to, to include further Emtree and free text terms in the title or abstract.

The search filter for costs is based on that of the McMaster University Health Information Research Unit filter, with further terms added to identify resource use and budget impact analyses.

Economic evaluations were unlimited by date. Costs and HCRU data were limited to those published in the last 10 years (2010+).

A single search strategy was developed to identify both economic evaluations and costs/HCRU studies. The search terms comprise population terms AND an economic or cost filter (no intervention terms).

The complete search strings are reported in Appendix 3, Section 17.3.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

The inclusion and exclusion criteria used to select studies from the literature are given in Table 68 below:

Table 68. Selection criteria used for health economic (and HCRU) studies

[8] http://www.slideshare.net/wichor

Inclusion criteria	
Population	MPS IVA (Morquio syndrome) patients, children or adults Mimic disease (hours of caregiving/health state)
Interventions	For CUAs • Enzyme replacement therapy, e.g. elosulfase alfa • No treatment/standard clinical management For cost/resource use data • No restriction or none
Outcomes	For CUAs Evaluation includes both costs *and* effectiveness/utility measures (need not necessarily report an ICUR, but needs to report QALYs) For cost/resource use data Budget impact Direct healthcare costs Indirect and societal costs • Productivity losses • Absenteeism • Presenteeism Patient/family/caregiver costs (including loss of income, travel, formal and informal care, out-of-pocket expenses) Caregiver burden Estimates of resource use including, but not limited to: hospitalisation, length-of-stay, admissions, readmissions, emergency room visits (intensive care unit), outpatients, procedures, etc.) Cost drivers including hospitalisation and length of stay Assumptions underpinning resource use
Study design	For economic: CUAs Economic evaluation within a clinical trial SR+ For cost/resource use: Unrestricted: any methodological design may be included, e.g. cross-sectional, retrospective cohort, national database analyses, etc. COI and BIA will be particularly good sources of data. WTP studies SR+
Date limits	Unlimited for CUAs

	Since 2010 for cost/resource use
Country	Unlimited for CUAs Europe (EU-27), UK, USA, Canada, Australia/New Zealand for cost/resource use
Perspective	Payer or societal
Time horizon	Lifetime (very short-term time horizon (≤1 year) studies will be excluded)
Publication type	Original articles Errata Technology appraisal documents, if original source not available elsewhere
Language	Electronic searching will **not** be limited by English language ++
Exclusion criteria*	
Publication type	e1 pub: Publication type not of interest
Duplicate	e1 dup: Duplicate/copy
Child abstract	e1/e2 child Child abstract or sub-study with no unique data
Languages ++	e2 lang: Full text in language outside of language capabilities. Non-English language article agreed between BioMarin and Vendor to be ineligible
Population	e1/e2 pop: Animal data Healthy volunteers Not MPS IVA or multiple sclerosis (if caregiver outcome)
Mixed populations	e1/e2 mix: Mixed population enrolled e.g. mixed MPS populations
Interventions / comparators	e1/e2 comp: For CUAs: Any ERT or no treatment/standard clinical management Gene therapy HSCT For cost/resource use: Unrestricted or none
Study design	e1/e2 design: Non-systematic reviews SRs/MAs + Pilot studies Case reports

	MEAs MCDA Social cost value analysis PK/PD study only Other types of economic evaluation, e.g. CEA, CMA, CCA, CBA In vitro studies
Outcomes	e1/e2 out: No outcome of interest
Date limits	No restrictions on CUAs 2010 onwards on cost/resource use data
Country limits	e1/e2 country No restrictions on CUAs Not Europe (EU-27), UK, USA, Canada, Australia/New Zealand for cost/resource use data
Perspective	e2 perspective Unclear perspective
Time horizon	e1/e2 time horizon Time horizon ≤ 12 months

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

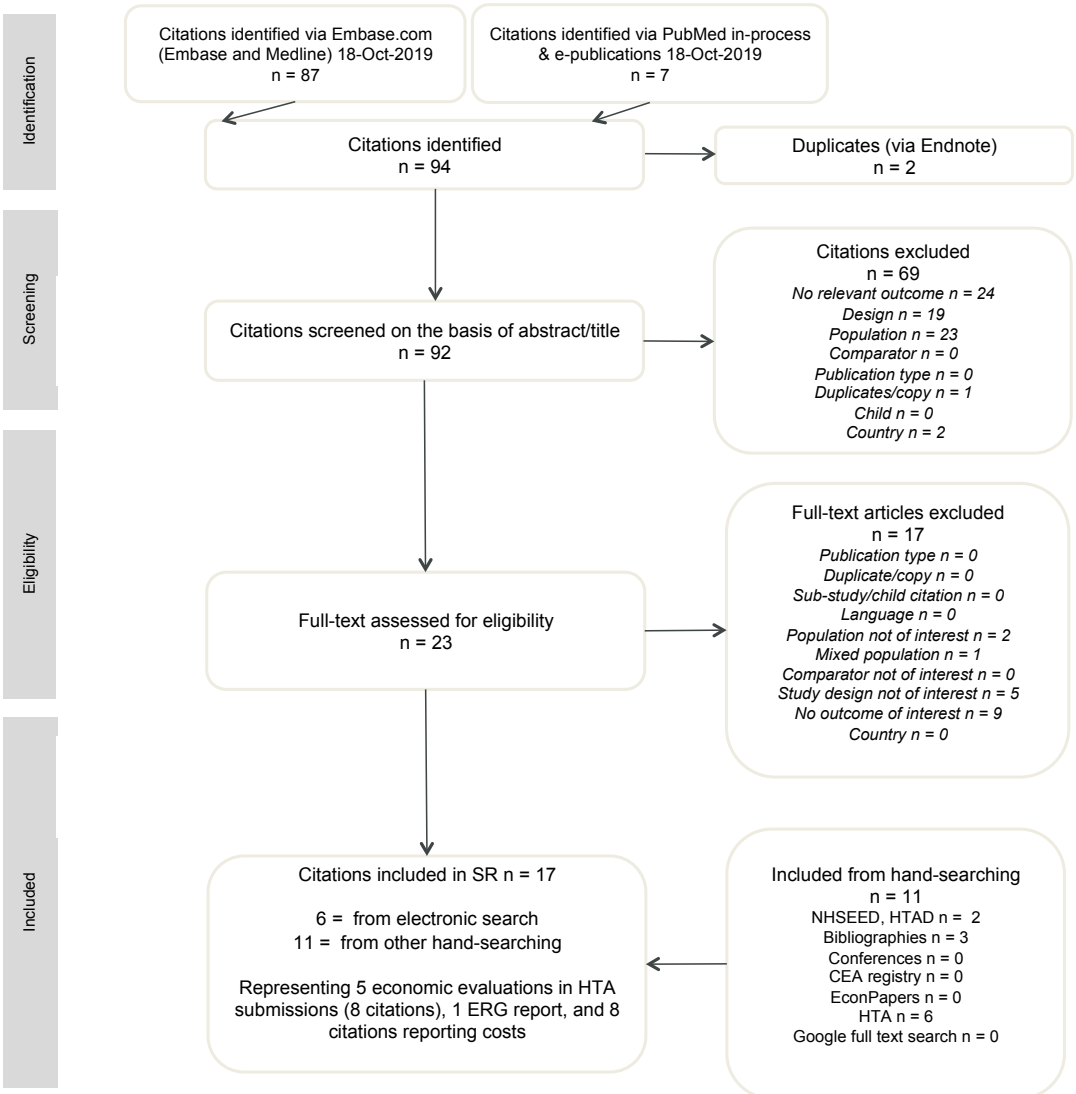
The electronic database searches identified 94 citations (87 from Medline/Embase, and 7 from Medline InProcess/e-publications). After duplicate removal in Endnote (2 citations), and after first pass (title/abstract) screening (69 exclusions, see Appendix 3 Table 144), 23 papers were screened at second pass. Following full paper review (17 exclusions, see Appendix 3, Table 145), 6 articles were included from electronic sources.(Corcoran et al., 2018; Lampe et al., 2014; Macaulay et al., 2016; Puckett et al., 2017; Taylor et al., 2019; Tomatsu et al., 2015). A further 11 articles were identified via hand-searching (AWMSG, 2016; CADTH, 2016a and 2016b; Cooper et al., 2015; Finnigan et al., 2018; IQWIG, 2017; NCPE, 2016; NICE, 2015, 2015b and 2015c; SMC, 2015). A total of 17 citations were, therefore, included in the SR (Table 69).

Table 69. Summary listing of included studies (n=17)

Author, Year	Title
(AWMSG, 2016)	Elosulfase alfa (Vimizim®). Reference No. 1084
(CADTH, 2016a)	Common Drug Review Pharmacoeconomic Review Report (Resubmission). Elosulfase alfa (Vimizim)
(CADTH, 2016b)	Common Drug Review Clinical Review Report (Resubmission). Elosulfase alfa (Vimizim)
(Cooper et al., 2015)	Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA: A Highly Specialised Technology Evaluation. Southampton Health Technology Assessments Centre (SHTAC)
(Corcoran et al., 2017)	Medical tourism in the metabolic world!
(Finnigan et al., 2018)	Home infusion with Elosulfase alpha (Vimizim(R)) in a UK Paediatric setting
(IQWIG, 2017)	[Elosulfase alfa (mucopolysaccharidosis type IVA) - assessment according to §35a (para. 1, sentence 11) Social Code Book V (new scientific findings)]
(Lampe et al., 2014)	Burden of disease suffered by caregivers of patients with Morquio syndrome type A: Results from a self-reported outcomes survey
(Macaulay, 2016)	Managed access agreements: A new model pathway for the reimbursement of non-oncology drugs in England approved under European adaptive pathways?
(NCPE, 2016)	Cost-effectiveness of elosulfase alfa (Vimizim®) for the treatment of Morquio A syndrome in patients of all ages
(NICE, 2015a)	Elosulfase alfa for treating mucopolysaccharidosis type IVa. Highly specialised technologies guidance [HST2]
(NICE, 2015b)	Elosulfase alfa for treating mucopolysaccharidosis type IVa - final evaluation determination
(NICE, 2015c)	Highly Specialised Technologies. Elosulfase alfa for treating mucopolysaccharidosis type IVa [ID 744]. Committee Papers.
(Puckett et al., 2017)	Enzyme Replacement Therapy with Elosulfase alfa for Mucopolysaccharidosis IVA (Morquio A Syndrome): Milestones and Challenges
(SMC, 2015)	Elosulfase alfa, 1mg/mL concentrate for solution for infusion (Vimizim®) SMC No. (1072/15)
(Taylor et al., 2019)	Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses: Past, Present, and Future
(Tomatsu et al., 2015)	Impact of enzyme replacement therapy and hematopoietic stem cell transplantation in patients with morquio a syndrome

The screening process is summarised in a PRISMA flow diagram (Figure 58).

Figure 58. PRISMA Flow-chart for study identification and selection of economic, cost and HCRU data



Abbreviations: CEA, cost-effectiveness analysis; CUA, cost-utility analysis; HTA, Health Technology Assessment; HTAD, Health Technology Assessment Database; NHS EED, National Health Service Economic Evaluation Database; SR, systematic review

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

There were no published studies of economic evaluations identified relevant to decision-making of England.

HTA assessments in England (Cooper et al., 2015, NICE, 2015a, NICE, 2015b, NICE, 2015c), Scotland (SMC, 2015), Wales (as in England) (AWMSG, 2016) Ireland (NCPE, 2016) and Canada (CADTH, 2016a, CADTH, 2016b) were identified and included. All models had a lifetime horizon: in Canada this was for 35 yrs, in England for a maximum of 100 years. The SMC model had 6 HSs (including death) and costs and QALYs were discounted at 3.5%, whereas in both the NICE and CADTH models there were 7 health states (Asymptomatic, No wheelchair use, Sometimes use wheelchair, Wheelchair-dependent, Paraplegic, Pre-death/End-stage and Death) and, for NICE, the base case discounting rate was 1.5% for costs and QALYs. This was instead of the usual 3.5% for the NICE reference case, which is as per the NICE methods for technology appraisal (section 6.2.19) when treating patients that would otherwise not survive, in pts who suffer from severely impaired conditions or when a condition lasts for >30 yrs. The NCPE model, with a discount rate of 5%, is less relevant to decision-making in England.

The Canadian, Irish and Scottish assessments were CUAs, reporting ICURs for ESA vs Standard of Care (SOC) of CAN $1,720,127/QALY in the base case, EUR €1,032,228/QALY and, including a PAS, GBP £829,870/QALY, respectively. The English assessment was a CCA, reporting costs and QALYs separately. In the (corrected) discounted base case, ESA resulted in 27.83 QALYs (total costs CIC) and SOC 9.75 QALYs and total costs GBP £618,812. The additional QALYs with ESA were, therefore, 18.18 in the base case.

The health economic (HE) conclusion following assessment by NICE was that elosulfase alfa yields clinical benefits in terms of improvement in survival and in QoL and that it is CE vs. SOC. Elosulfase alfa was recommended for

funding in England with a 5-year MAA (from December 2015). The MAA was adopted (elosulfase alfa recommended) by NHS Wales 24-Feb-2016 and has now been extended by 12 months until December 2021. Elosulfase alfa was recommended and is reimbursed in Ireland.

Elosulfase alfa was not recommended, due to uncertainties around CE, in Scotland. Canada concluded that there remained uncertainties around the CE of elosulfase alfa.

A summary of these models and the results is provided in Table 70.

Table 70. Summary list of all economic evaluations involving costs (Table D2)

Study name (year)	Location	Cost year	Model summary	Pt population, mean (median) age, yrs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER per QALY gained
AWMSG, 2016 (AWMSG, 2016) HTA	Wales	NR	NR (AWMSG accepted NICE decision work)	NR	NR	NR	NR
CADTH 2016a,b (CADTH, 2016a, CADTH, 2016b) HTA	CAN	2015	Lifetime (35 yrs) Markov model, payer perspective, 1 yr cycle length, discounts unclear, 6 HSs (Asymptomatic, No wheelchair use, Sometimes use wheelchair, Wheelchair-dependent, Paraplegic, Pre-death) and Death, NR if half-cycle correction used	NR, BL distribution, age and weight of pts in each HS based on MOR-001 natural history study	ESA total QALYs: 12.69 BSC total QALYs: 6.40 Incremental QALYs: 6.29	ESA total costs: $10,851,054 BSC total costs: $31,809 Incremental cost: $10,819,245	BC ESA vs BSC: $1,720,127

Study name (year)	Location	Cost year	Model summary	Pt population, mean (median) age, yrs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER per QALY gained
Cooper, 2015 (Cooper et al., 2015) ERG report and erratum (NICE HTA)	England	2011/2012	Lifetime Markov model, payer (NHS) perspective, 1 yr cycle length, costs and QALYs discounted at 1.5%, 6 HSs (Asymptomatic, No wheelchair use, Some wheelchair use, Wheelchair-dependent, Paraplegic, End-stage) and Death, half-cycle correction used	NR, MOR-001 used as proxy for prevalent population in England	ESA QALYs: 27.83 (discounted, corrected in erratum report from original ERG report value of 27.93) SOC QALYs: 9.75 (discounted) ESA vs SOC additional QALYs: 18.18 (discounted)	ESA total costs lifetime: CIC SOC total costs lifetime: £618,812	NR (CCA)
NCPE, 2016 (NCPE, 2016) HTA	Ireland	NR	Lifetime model, payer perspective, cycle length NR, costs and QALYs discounted by 5%, no. of HSs NR, use of half-cycle correction NR	NR, based on MOR-001 natural history study	ESA QALYs: 14.97 SOC QALYs: 7.07	ESA costs: €8,187,681 SOC costs: €33,080	ESA vs SOC: €1,032,228/QALY

Study name (year)	Location	Cost year	Model summary	Pt population, mean (median) age, yrs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER per QALY gained
NICE, 2015a/b (NICE, 2015a, NICE, 2015b, NICE, 2015c) HTA	England	NR	Lifetime (100 yrs max) Markov model, NHS/PSS payer perspective, 1 yr cycle length, costs and QALYs discounted at 1.5%, 7 HSs (Asymptomatic, No wheelchair use, Some wheelchair use, Wheelchair-dependent, Paraplegic, End-stage and Death), half-cycle correction NR	NR, based on MOR-001 natural history study, which was a younger group with less advanced disease than people with MPS IVA in England	ESA QALYs: 27.93+ (discounted) SOC QALYs: 9.75 (discounted) ESA vs SOC additional QALYs: 18.18 (discounted) ESA QALYs: 42.57 (undiscounted) SOC QALYs: 12.18 (undiscounted) ESA vs SOC additional QALYs: 30.39 (undiscounted)	ESA total costs lifetime: CIC ESA acquisition costs lifetime: £14,014,636 SOC total costs lifetime: £618,812	NR (CIC)

Study name (year)	Location	Cost year	Model summary	Pt population, mean (median) age, yrs	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER per QALY gained
SMC, 2015 (SMC, 2015) HTA	Scotland	NR	Lifetime model, NHS Scotland/PSS payer perspective, cycle length NR, costs and QALYs discounted at 3.5%, 6 HSs (Asymptomatic, No wheelchair use, Some wheelchair use, Wheelchair-dependent, End-stage and Death), half-cycle correction NR	NR	Incremental QALYs: 9.91	ESA cost/yr (aged 2-5 yrs with mean weight 14kg from MOR-007 study): £192,504 excluding PAS ESA cost/yr (aged >5 yrs with mean weight 27kg from MOR-001 study at 2 yrs f-up): £352,924 excl. PAS Incremental cost: £8,242,197	ESA vs BSC, including PAS £829,870 / QALY

Abbreviations: BC, base case; BL, baseline; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health CAN, Canada; CCA, cost-consequence analysis; CIC, Commercial-in-confidence; ERG, Evidence Review Group; ESA, elosulfase alfa; excl., excluding; HS, health state; HTA, health technology appraisal; ICER, incremental cost-effectiveness ratio; MPS, mucopolysaccharidosis; NCPE, National Centre for Pharmacoeconomics (Ireland); NHS, National Health Service (England); NICE, National Institute of Health and Care Excellence; no., number; NR, not reported; PAS, Patient Access Scheme; PSS, Personal Social Services (England); QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; SOC, standard of care; yr, year; yrs, years
+ Corrected in erratum to ERG report to 27.83

Table 71. List of new relevant articles (November 2020)

Author, Year	Title
(Åkesson et al., 2019)	PRO116. Understanding the role of real-world evidence in health technology assessment for orphan drugs
(Balijepalli et al., 2020)	Can standard health technology assessment approaches help guide the price of orphan drugs in Canada? A review of submissions to the Canadian agency for drugs and technologies in health common drug review.
(Darbà and Marsà, 2020)	Current status and use of resources of lysosomal storage diseases: Analysis of a Spanish claims database
(Jain et al., 2020)	Biodegradable polyethylene glycol hydrogels for sustained release and enhanced stability of rhGALNS enzyme
(Mitchell et al., 2019c)	Clinical Practice Guideline: Tonsillectomy in Children (Update)—Executive Summary

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

No quality assessment of models using the Drummond Checklist (Drummond and Jefferson, 1996) was performed because no full-text model publications were identified. A summary of the limitations identified in the HTAs by CADTH, NCPE, NICE and SMC is available in the Data Extraction Table (DET)[9].

[9] ECO – Population & Intervention tab, column S.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The population included in the model is patients diagnosed with MPS IVA, as per the indication in the SPC (SPC, 2014): *elosulfase alfa is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.*

The population characteristics and key outcomes assumptions of the cost-utility model are based in the data collected from patients enrolled in the Managed Access Agreement and its application for the model is described in the next items of this section (clinical results reported in the section 9.6.1.2.1).

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

The technology used is elosulfase alfa 1 mg/ml concentrate solution for infusion, indicated for the treatment of MPS IVA.

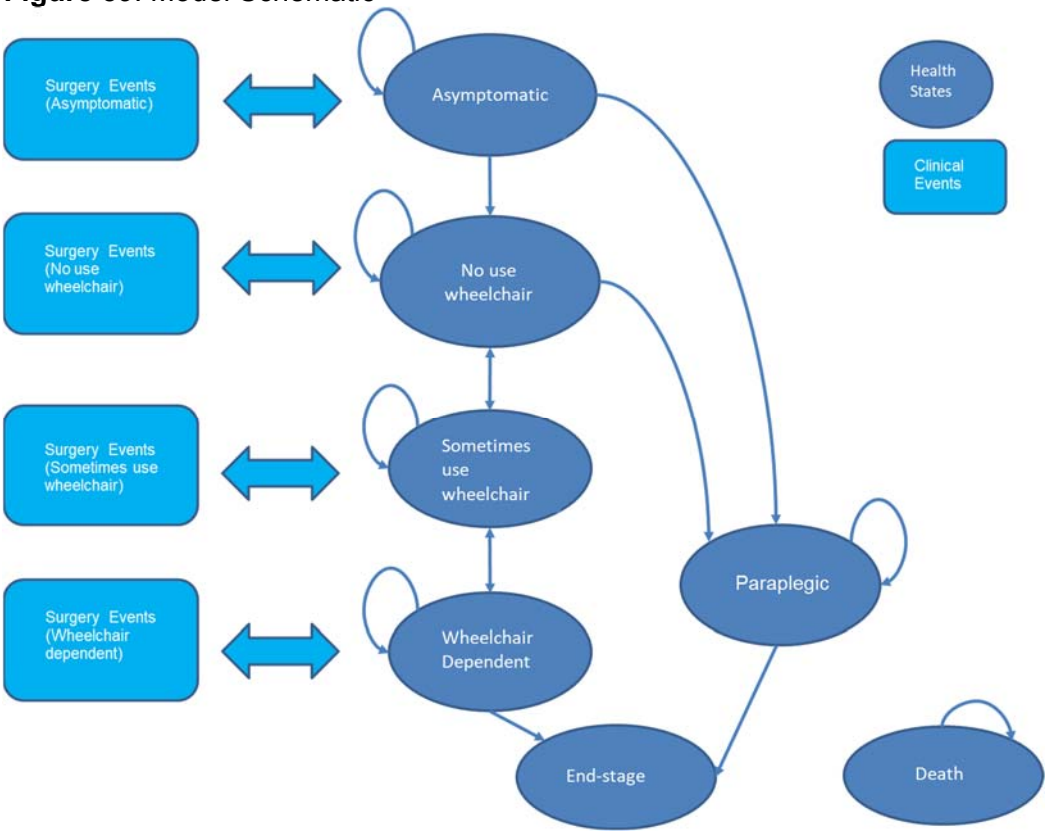
The comparator is best supportive care. Elosulfase alfa is the only treatment available which addresses the underlying cause of MPS IVA.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

A Markov disease model was developed that depicts the lifelong disease progression of patients who are diagnosed with MPS IVA. The core model was built for the NHS England setting, and therefore also adheres to the NICE highly specialised technologies guidance. The model schematic diagram is presented below:

Figure 59: Model Schematic



12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The modelling approach is the same of the economic model submitted and accepted by the NICE Committe in the HST appraisal. The Markov disease

model is in line with the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidance (Caro et al., 2012).

The structure of the model uses distinct health states to represent different stages of the disease and compares treatment with elosulfase alfa to best supportive care (natural history). The base-case analyses were conducted from the NHS and PSS perspective. The robustness of the base case point estimates was addressed within extensive deterministic and probabilistic sensitivity analyses as well as in a scenario analysis.

The model was designed with six mutually exclusive and collectively exhaustive health states, and an absorption state of death which could be entered from any health state (see Section 6 for information on mortality).The health states are based on the clinical manifestations of the disease over time, in particular the use of wheelchairs which has shown to have a significant impact on the quality of life and independence for patients.

1. Asymptomatic: Diagnosed MPS IVA patients who have not yet developed severe musculoskeletal complications or experience limitations in endurance and cardiopulmonary function. These patients may have some soft tissue complications such as hearing problems requiring ear tube placement and breathing problems requiring tonsillectomy and/or adenoidectomy.

2. No use of wheelchair: These are MPS IVA patients who have started to develop some musculoskeletal complications and limitations in endurance but do not need WC support.

3. Sometimes use wheelchair : These are MPS IVA patients who have developed significant issues limiting endurance such as pain, fatigue and musculoskeletal manifestations. These patients require some WC use to help manage symptoms of disease and maintain independence.

4. Wheelchair dependent : These are MPS IVA patients who have developed major limitations to endurance driving to WC dependency which tend to be increased pain, fatigue and skeletal manifestation.

These patients are dependent on WC for all mobility but may not necessarily be WC bound (C. J. Hendriksz *et al.*, 2014).

5. Paraplegic health state: These are MPS IVA patients who become paraplegic due to surgical complications.

6. End-stage is defined as when patients are always in a WC and also require mechanical ventilation.

Cycle length and half-cycle correction

The cycle length considered in the model is one year. One year is a sufficiently long time period to allow for events to occur (e.g. change in 6MWT) and subsequently the cost of care to be evaluated for patients. In addition, one year may be sufficient to determine whether or not a patient will respond to treatment. As it is unknown when a decline or surgery could occur, half-cycle correction is applied throughout the model.

Validation of de novo cost-effectiveness analysis

The model structure and assumptions were validated by a group of clinical experts in England in November 2020.

The model is reflective of clinical experience with elosulfase alfa, as the outcomes observed in the real world data collected as part of the MAA (Mukherjee et al., 2019a, Mukherjee et al., 2020), which demonstrate that patients who have been treated with elosulfase alfa show initial improvements across multiple outcomes, including endurance, lung function, and cardiac function, which corresponds to patients spending significant periods of time in the symptomatic no wheelchair use state, and slowly moving to sometimes and wheelchair dependent states. Paraplegia has not been seen frequently in clinical practice and few patients have entered the end-stage since treatment began. This is compared to natural history data where it is expected to see an annual decline in mobility and lung function and therefore a significantly more rapid decline in health.

Perspective

The model base-case provides a NHS and PSS perspective. A scenario analysis of a social perspective is also provided.

Starting population

The baseline characteristics of patients who started treatment under the MAA (defined as 'ERT-Naïve patients'), is the main source for the starting population in the model. The data was collected as part of terms of the Managed Access Agreement, defined as 'MAA Dataset' and should reflect the future population to be eligible for the treatment in the United Kingdom.

The patient population started in the model according to their health state as described in Table 72. Patients were divided according to the Wheelchair dependency as captured by the MPS-HAQ questionnaire (question 33). The average age and weight at enrolment in the MAA are determined by health states and assigned as a starting assumption. The age of patients was important to determine background generalised mortality and weight was assigned as a weighted average per health state to account for patient heterogeneity, where all patients suffer a severe disease but progress at different rates.

Based on the limited baseline information collected regarding asymptomatic patients, the same assumption in the original submission based in the MOR-001 baselines remains.

Table 72. Proportion of starting cohort in each wheelchair health state and baseline data (MAA dataset [redacted]) [Asymptomatic patients, (Harmatz et al., 2013)]

Health State	Proportion of patients	Average starting age	Average starting Weight
Asymptomatic	4.9%	0 years	12.30 kg
No wheelchair use	39.8%	12.9 years	21.36 kg
Sometimes use wheelchair	50.0%	14.0 years	22.24 kg
Wheelchair dependent	5.3%	24.0 years	44.93 kg

End-stage	0%	n.a	n.a

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table 73: Model assumptions

S No.	Assumption	Source
1.	Patients treated with elosulfase alfa would have a 5-year delay in transition from the 'asymptomatic' state to the 'no wheelchair use' health state due to delay in development of non-reversible complications and arrested disease progression	▪ Clinical opinion obtained from Expert Panel by a Delphi process (see section 12.2.5) ▪ Experiences from other MPS diseases, specifically: ▪ Furujo, M. et al, Enzyme replacement therapy attenuates disease progression in two Japanese siblings with mucopolysaccharidosis type VI: 10-Year follow up, Mol Genet Metab Rep. 2017 Dec; 13: 69–75 (Furujo et al., 2017); and ▪ McGill J.J. et al. Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age-a sibling control study. Clin Genet. 2010 May;77(5):492-8 (McGill et al., 2010)
2.	Improved clinical outcomes translates into greater HRQoL in treated patients versus untreated patients for each health state	▪ Lampe C, 2014 "Relationship between Patient-Reported Outcomes and Clinical Outcomes in Patients with Morquio Syndrome A" ▪ Clinical opinion obtained from Expert Panel by a Delphi process (see section 12.2.5) ▪ Clinical results of the real-world data collected in the MAA (see section 9.6.1.2.1)
3.	Caregivers in each health state would suffer from a significant disutility for caring for a patient requiring significant care.	▪ Caregiver disutility are mapped from patients suffering similar states of limited mobility in MS as described in Item 10.1.7 (Acaster et al., 2013, Gani et al., 2008)

4.	Caregiver costs are considered for each health state as supporting the care of patients	▪ Caregiver time and associated costs are taken from the MPS IVA caregiver burden of disease study (Hendriksz et al., 2014c) and standard PSSRU costs (Curtis and Burns, 2019)
5.	0.1L annual decline in FVC for untreated patients in wheelchair dependent health state due to deteriorating pulmonary function	▪ Clinical opinion obtained from Expert Panel by a Delphi process (see section 12.2.5)
6.	2-year duration in end-stage health state for all patients	▪ Clinical opinion obtained from Expert Panel by a Delphi process (see section 12.2.5)
7.	Delay in orthopedic surgery in patients treated with elosulfase alfa versus untreated patients	▪ MOR-005 Phase 3 Extension Study
8.	Utility decrement during recovery period following surgery	▪ Clinical opinion obtained from Expert Panel by a Delphi process
9.	Elosulfase alfa-treated patients would have quicker recovery rates from surgery versus untreated patients	▪ Clinical opinion obtained from Expert Panel by a Delphi process
10.	6.84 m 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	▪ Longitudinal analysis of the MOR001 2-year data for the 6MWT following a cohort matched to the inclusion criteria in MOR004
11.	Slowed rate of progression of disease in long-stabiliser patients and mild decliner	▪ Clinical opinion obtained from Expert Panel by a Delphi process ▪ Clinical results of the real-world data collected in the MAA (see full description in section 9.6.1.2.1)

12.	Increasing dependency on wheelchairs over two years in an untreated population with progressing disease.	▪ Longitudinal analysis of the MOR001 2-year data for the MPS HAQ following a cohort matched to the inclusion criteria in MOR004.
13.	Reduced dependency of a wheelchair following the first 2 years of elosulfase alfa treatment.	▪ Clinical results of the real-world data collected in the MAA (see section 9.6.1.2.1)
14.	Mortality relative risk for untreated patients versus treated patients.	▪ Survival benefit reported in a long-term study in MPS VI was used as a surrogate for the relative risk of untreated patients to be 2.38 greater than that of treated patients (Quartel et al., 2018).

MPS VI a relevant analogue for MPS IVA

As can be seen in Table above, the cost utility analysis presented here assumes that MPS VI still is a relevant analogue of MPS IVA as discussed in the HST2 appraisal.

12.1.6 Define what the model's health states are intended to capture.

Health state definitions

Average 6MWT scores were assigned to the no wheelchair and sometimes wheelchair health states. This was based on the mean 6MWT scores of all patients who reported not using wheelchair and using wheelchair sometimes at baseline in the MOR-001 natural history study respectively (Table 74). Similarly, average FVC score was assigned to the wheelchair dependent and paraplegic health states based on mean FVC of patients who reported always using wheelchairs at baseline in the MOR-001 study.

Table 74: Average 6MWT and FVC values per wheelchair group in MorCAP study (Harmatz 2013)

	No WC	Sometimes uses WC	Wheelchair dependent

6MWT (m)			
Mean	289	180	31
95% CI	270 – 308	154 – 207	17 – 46
FVC (L)			
Mean	1.34	1.15	1.03
95% CI	1.32 – 1.36	1.14 – 1.16	0.98 – 1.08

Exit 6MWT values were assigned to the no wheelchair use and sometimes use wheelchair health states based on the upper 95% confidence interval CI_{95} of the health state they would exit into. Based on clinical opinion from UK clinical experts an exit FVC score of 0.3L was assigned to the "wheelchair dependent" and "paraplegic" health states. The rationale for this was that patients would require continuous mechanical ventilation when their FVC is 0.3L or less and, as such, would transition to the end-stage health state (Table 75).

Table 75: Mean and exit scores for wheelchair health states

Health State	Value	Unit	Source
Never use WC			
Annual average loss in 6 Minute Walk Test	6.84	m	MOR-001
Mean score for patients in this health state	289	m	MOR-001
Exit Score for transition to Sometimes use WC health state	207	m	MOR-001
Sometimes use WC			
Annual average loss in 6 Minute Walk Test	6.84	m	MOR-001
Mean score for patients in this health state	180	m	MOR-001
Exit Score for transition to Always WC health state	46	m	MOR-001
Wheelchair dependent health state			
Mean FVC level for patients in this health state	1.0	L	MOR-001
Average annual loss in FVC measure	0.1	L	Clinical Opinion
Exit FVC level for transition to Pre-death health State	0.5	L	Clinical Opinion

Caregiver burden

In addition, per health state caregiver lost working hours have been sourced from the burden of illness study which showed that the number of caregiving

hours increased with increasing wheelchair dependency (Hendriksz et al., 2014a) as presented in Table 76 below.

In the base case, it is assumed that 50% of the caregiver hours will be covered by professional carers and 50% by family members. The standard cost of £28 per hour of care is taken from PSSRU 2019 (*home care worker, face to face*) (Curtis and Burns, 2019)

Table 76: Number of hours of caregiving per health state per day

Health State	Hours of caregiving	Source
Asymptomatic	1.5	*Clinical opinion assumed to be same as no wheelchair use health state*
Never use wheelchair	1.5	*Hendriksz 2014d*
Sometimes	4.0	*Hendriksz 2014d*
Wheelchair dependent	14.0	*Hendriksz 2014d*
Paraplegic	14.0	*Clinical opinion assumed to be the same as wheelchair dependent health state*
Pre-death	14.0	*Clinical opinion assumed to be the same as wheelchair dependent health state*

In additional consideration of the caregiver burden, caregiver dis-utilities are taken following the approach described in Section 10.1.9. The approach is to use caregiver disutility values taken from Acaster et al, 2013 who reported the disutility for carers of patients with Multiple Sclerosis using the Patients Determined Disease Steps (PDSS) questionnaire. The values selected from this study were those for PDSS states with utility values closest to the MPS IVA patients in each health state. These are reported in Table 65 in section 10.1.9 above.

Primary Outcome Measure

The model assumes that patients follow a certain pathway with progression through the model determined by their current health state. Progression through the model is based on the following four different outcome measures:

1. **Time to symptom development:** This outcome measure is applicable in all cycles to patients in the "asymptomatic" health state only. "Asymptomatic" patients would progress to the "no wheelchair" health state when they reach the age of 3, by which point they would have developed clinical manifestations of the disease leading to endurance limitations and musculoskeletal complications (Montaño et al., 2007).

2. **Change in wheelchair use:** This outcome measure is applicable to the first cycle only for patients in the wheelchair health states (i.e. no wheelchair use, sometimes wheelchair use, and wheelchair dependent health states) (Table 77). It is based on the observed changes in wheelchair status (wheelchair shift data) from baseline to last-follow of the MAA dataset (ERT-Naïve Population) and MOR-001 natural history study as captured by the MPS HAQ questionnaire (33 and 33a).

Table 77. Wheelchair progression in MPS IVA patients ERT-Naïve patients from the MAA treated with elosulfase alfa 2.0mg/kg/week versus untreated patients (MorCAP study).

MAA dataset, November 2019				
Last Follow-up	**Baseline**	**No use WC**	**Some use WC**	**WC dependent**
	No use WC	56%	6%	0%
	Some use WC	38%	78%	0%
	WC dependent	6%	17%	100%
MOR-001 (based on 2-year data)				
2-years assessment	Baseline	No WC	Occ. WC	Always WC
	No use WC	82%	18%	0%
	Some use WC	4%	76%	20%
	WC dependent	0%	22%	78%

Following treatment, patients' wheelchair status would improve (reduced wheelchair dependency), stabilise (maintained level of wheelchair dependency) or worsen (increased wheelchair dependency). Patients whose wheelchair status improved had a corresponding backward shift reflecting the reduced wheelchair dependency. Those whose wheelchair status stabilised remained in the same wheelchair health state. While patients who worsened, progressed to the next health state in relation to the increased level of wheelchair dependency. Based on clinical opinion, a proportion of patients whose wheelchair status worsens would discontinue elosulfase alfa treatment after two cycles of the model due to treatment non-response. All other patients would continue treatment with elosulfase alfa.

In the absence of long-term data on wheelchair progression, from the second cycle onwards progression through the model is based on change in 6MWT/FVC.

- **6MWT:** This outcome measure is applicable for the second cycle onwards for patients in the "no wheelchair" and "sometimes wheelchair" health states. These patients would progress based on a 6.84 metres annual decline in their 6MWT until they reach the "wheelchair dependent" health state. This is based on 2-year longitudinal data from the MorCAP study which showed progressive annual decline in 6MWT in MPS IVA patients.

- **FVC:** As patients in the “wheelchair dependent” and “paraplegic” health states may be unable to perform the 6MWT, disease progression through the model is by a 0.1L decline in their FVC. This is based on expert UK clinical opinion that MPS IVA patients see a progressive decline in their pulmonary function once they have stopped growing due to progressive worsening of restrictive and obstructive lung disease.

Average 6MWT scores were assigned to the no WC and sometimes WC health states. This was based on the mean 6MWT scores of all patients who reported not using WC and using WC sometimes at baseline in the MOR-001 natural history study respectively (See Table 74). Similarly, average FVC score was assigned to the WC dependent and paraplegic health states based on mean FVC of patients who reported always using WCs at baseline in the MOR-001 study.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Table 78. Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	LIfetime	MPS IVA is a life-limiting, lifelong disease and patients will continue to need management and/or treatment for the whole of their lives.	
Discount of 3.5% for costs	1.5%	Although the NICE reference case discount rate is 3.5% for both costs and health effects, the BioMarin model applies a discount rate of 1.5% to both cost and effects on the assumption that treatment with elosulfase alfa restores people who would otherwise die or have a very severely impaired life to full or near full health.	Section 6.2.19 NICE Guide to the Methods of Technology Appraisal 2013.
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	
Cycle length	I year	This is considered a reasonable timeframe over which to make a clinical assessment	UK expert clinical opinion
NHS, National Health Service; PSS, Personal Social Services			

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

Comparator

There are no licensed treatment options other than elosulfase alfa for the treatment of MPS IVA. In order to provide a meaningful assessment of the cost-utility of elosulfase alfa, the comparison will be made with the current standard of care without elosulfase alfa vs. the future standard of care with elosulfase alfa (which is also considered in the SOP for England described in section 8).

Data from the natural history MOR-001 study has been used for the “standard care strategy” arm population. The study is a longitudinal study in which clinical outcomes have been prospectively collected over 2 years under real

life settings in MPS IVA patients unexposed to elosulfase alfa. This represents the largest collection of natural history data in any MPS disease with 325 patients enrolled at baseline.

Although elosulfase alfa was compared to placebo in the 24 week MOR-004 Phase 3 clinical trial, due to the short time frame, the prohibition of surgery and the artificially high level of care received during this study with weekly clinical visits, the results from the placebo arm of the trial are not representative of current standard of care.

Mortality

To reflect the reduced life expectancy of untreated MPS IVA patients relative to the normal population, mortality is implemented as a relative risk compared to background mortality.

The relative risk of mortality of untreated patients was assumed to be 2.38 greater than that of elosulfase alfa treated patients. This is based on the assumption that that treatment with elosulfase alfa would lead to the same long-term survival benefit to that observed with galsulfase in the treatment of MPS VI. Results of a 15-year study of MPS VI have shown that the rate of mortality for Naglazyme (galsulfase) treated patients was 2.38 times less than that of untreated patients (i.e. 24.0% versus 57.1%) (Quartel et al., 2018). This assumption of similar survival benefit between ERT treated MPS disorders is supported by evidence indicating enzyme replacement therapy treatments of MPS conditions are associated with similar mechanisms of improvement in pulmonary function, with the improvement in pulmonary function observed in elosulfase alfa comparable to the improvements observed after treatment of other MPS with ERTs in a similar time frame (FVC improved by 15.3% after 72 weeks of treatment with elosulfase alfa versus 14.4% at week 72 for naglazyme treated MPS VI patients (Harmatz et al., 2010) and 19.2% at 70 weeks for iduruslfase treated MPS II patients (Muenzer et al., 2011). To ensure that the mortality risk of elosulfase alfa treated patients would never be less than that of the normal population, we

have assumed that they have the same mortality risk as that of the normal population (Table 79).

Table 79. Mortality Relative Risk

	Relative risk	
	Natural history	**Elosulfase Alfa**
Asymptomatic	2.377	1.000
No wheelchair use	2.377	1.000
Sometimes use wheelchair	2.377	1.000
Wheelchair dependent	2.377	1.000
Paraplegic	2.377	1.000

For sensitivity analysis, an alternative approach to mortality was modelled. In this approach a relative risk ratio compared to background mortality is applied to each health state based on the % decrement in FVC1, which has been shown to have a linear relationship with mortality in the general population, with relative risk for mortality of 1.12 for a 10% decrement in FVC (Neas and Schwartz, 1998).

Average values of % FVC were assigned to the wheelchair health states based on the mean % FVC values of all patients who reported being in that wheelchair health state at baseline in the MOR-001 natural history study respectively (see sheet FVC MorCAP Calcs). The % FVC values were obtained for each patient by dividing the absolute FVC values by the predicted FVC value. As recommended by the European Respiratory Society, the reference equation of European Community for Steel and Coal study were used in calculating the predicted FVC values (Quanjer et al., 1993). These equations are detailed below.

European Respiratory Society reference equation (Quanjer et al., 1993)

- For males: (5.76*height) - (0.026*age) - 4.34
- For females: (4.43*height) - (0.026*age) – 2.89

As asymptomatic and end-stage patients are not included in the MORCAP natural history study, the mean %FVC for these health states were based on

clinical opinion. Asymptomatic patients were assumed to have a 100% FVC, while patients in end-stage were assumed to have a 10% FVC (see Table 80).

Table 80. FVC decrement and mortality relative risk for untreated patients (standard care strategy)

	FVC%		Relative Risk Mortality
	MOR001	% Decrement	
Asymptomatic	100%	0%	1.00
No wheelchair use	25%	75%	2.34
Sometimes use wheelchair	23%	77%	2.39
Wheelchair dependent	18%	82%	2.53

To reflect the impact of elosulfase alfa treatment on the mortality of an MPS IVA patient, a further adjustment was made to the calculated mortality rate of the untreated patient. Adjustment was based on an improvement factor derived from long-term data from the MOR002/100 trial data showing a 16.5% improvement in FVC versus baseline over 3 years treatment with elosulfase alfa. The model uses the Bisection method to evaluate the Improvement factor. The FVC for the treated arm and associated mortality relative risk are shown in Table 81.

Table 81. FVC and mortality relative risk - treated patients (elosulfase alfa + standard care strategy)

	FVC%		Relative Risk Mortality
	Treated	% Decrement	
Asymptomatic	100%	0%	1.00
No wheelchair use	46%	54%	1.85
Sometimes use wheelchair	42%	58%	1.93
Wheelchair dependent	33%	67%	2.14

The mortality relative risk for both the treatment and natural history arm for each health state are summarised in Table 82. It has been assumed that the relative risk in mortality is the same for wheelchair dependent and paraplegic patients.

Table 82. Mortality Relative Risk

	Relative risk

	Natural history	Elosulfase Alfa
Asymptomatic	1.000	1.000
No wheelchair use	2.340	1.955
Sometimes use wheelchair	2.387	2.020
Wheelchair dependent	2.521	2.208
Paraplegic	2.521	2.208

It should be noted that the FVC improvement for treated patients has been made flexible in the model as input changes to the FVC improvement (currently 16.5% in 3 years) automatically changes the treated mortality relative risks. Equally, if the transition probabilities for treated patients are altered in the "Efficacy" section the FVC mortality improvement relative risks are automatically updated to reflect the change in underlying FVC difference between treated and untreated patients due to the FVC assumptions for each health state.

Surgery

In each health state a proportion of patients would undertake 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 (for example, relating to anaesthesia, the complexity of spinal or cervical surgery, or because their cardio-pulmonary function is already compromised) leading to paraplegia or death. Patients who become paraplegic will enter the "paraplegic" health state.

Surgeries were treated as first cycle events with patients undertaking surgery at the beginning of the health state (start of the model for asymptomatic health state). Although some patients might have the same surgeries, given the infrequency of this occurrence, the model assumes patients would have not repeat the same surgery in the same health state. After surgery patients enter a recovery period during which they have a reduced quality of life. After this

recovery period has elapsed, they would return back to the same health state (unless they have already moved to the paraplegic health state, or have died).

The proportion of each type of surgery per health state, rates of surgical complications, the duration and utility decrement of the recovery period are based on clinical opinion from UK experts obtained via the Delphi process (Table 83 and Table 84). It is important to note that any surgery with the need for general anaesthetic and/or patient movement in a surgical room can be a risk as these patients have compromised airways and delicate spines.

Table 83. The proportion of patients receiving surgery for each health state[10]

Surgery	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent
Cervical Fusion Operation	37.5%	37.5%	0.0%	0.0%
Genu Valgum surgery	0.0%	0.0%	41.0%	0.0%
Spinal decompression surgery	0.0%	0.0%	40.0%	0.0%
Hip surgery	0.0%	0.0%	0.0%	6.8%
Lower spine surgery	0.0%	23.0%	0.0%	0.0%
Aortic valve replacement	0.0%	0.0%	0.0%	15.0%
Tonsillectomy	43.0%	0.0%	0.0%	0.0%
Ear tube placement	36.0%	0.0%	0.0%	0.0%
Corneal al replacement	3.4%	0.0%	0.0%	0.0%
Cataract surgery	3.4%	0.0%	0.0%	0.0%

Table 84. Outcomes following surgery based on expert clinical opinion

Surgery	Successful	Paraplegic	Death
Cervical Fusion Operation	78%	10%	12.0%

[10] The proportion of patients undertaking each surgery is based on MorCAP Baseline Characteristics (Harmatz 2013). While for patients undertaking each surgical procedure, the probability of undertaking it in each health state was based on expert clinical opinion.

Genu Valgum surgery	94%	0%	5.8%
Spinal decompression surgery	90%	0%	10.2%
Hip surgery	94%	0%	5.8%
Lower spine surgery	94%	0%	6.4%
Aortic valve replacement	84%	0%	16.0%
Tonsillectomy	98%	0%	2.3%
Ear tube placement	98%	0%	2.1%
Carpal Tunnel Surgery	98%	0%	2.1%
Corneal replacement	98%	0%	2.1%
Cataract surgery	78%	10%	12.0%

Pre-medications and adverse events

In the model, all patients receive pre-medication prior to receiving infusion. This is based on the MOR-004 study, which showed that nearly all subjects (98.3%) reported use of pre-medications for infusion. The type of pre-medication and proportion of patients receiving the drug are all sourced from the MOR-004 clinical trial results (MOR-004). The costs of these drugs are assumed to be included in the costs of hospitalisation during infusion of elosulfase alfa (see Table 85).

Table 85. Pre-medication drug used in at least 5% of patients receiving Elosulfase Alfa (2.0mg/kg/week) in MOR-004 clinical trial (MOR-004 CSR)

Drugs	Percentage of Patients*
Paracetamol	56.9%
Loratadine	34.5%
Desloratadine	13.8%
Prednisolone/ Prednisone	25.9%
Hydrocortisone	8.6%
Prednisolone Sodium Succinate	6.9%
Hydrocortisone Sodium Succinate	5.2%
Ranitidine/Ranitidine Hydrochloride	25.9%
Cetirizine/Cetirizine hydrochloride	22.4%
Diphenhydramine /Diphenhydramine Hydrochloride	17.2%
Clemastine Fumarate	6.9%
Chlorphenamine/ chlorphenamine maleate	12.0%

Hydroxyzine	8.6%
Emla/Lidocaine	6.9%
Ibuprofen	5.2%

*Total proportion of patients might add up to more than 100% as patients might receive more than one pre-medication.

Elosulfase Alfa Treatment Effect

Patients in all health states, except the end-stage health state, would be eligible for treatment with elosulfase alfa. Based on evidence from the pivotal trial and extension study (MOR004/005), long-term experiences based on real-world evidence (MAA dataset and MARS study) and clinical opinion, BioMarin has assumed that treatment of MPS IVA patients with elosulfase alfa would lead to the following modelled benefits:

1. **Delay the development of musculoskeletal complications by 5 years**
   This is based on clinical opinion the delay in developmental of symptoms seen in asymptomatic MPS I, II and VI patients initiated on ERT is an MPS class effect which would be also seen in asymptomatic MPS IVA patients treated with elosulfase alfa. This is also supported by evidence from several sibling case studies in MPS I, II and VI patients, which showed that younger siblings initiated on therapy whilst asymptomatic did not develop significant clinical manifestations of their disease such as musculoskeletal complications, cardiac disease and corneal clouding after up to 10 years of ERT treatment. However, at the equivalent age, the older sibling with the same disease phenotype already had these complications well established. Clinical opinion is that this is an MPS class effect and that treatment of asymptomatic MPS IVA patients with elosulfase alfa would delay the development of musculoskeletal complications by 5 years.

2. **Reduction in wheelchair dependency and wheelchair progression based on wheelchair shift data**
   A comparison of wheelchair shift patterns from the MAA dataset and MOR-001 over a similar time frame shows that treatment of MPS IVA with

elosulfase alfa leads to a reduction in wheelchair use and a reduced rate of disease progression (Table 77).

3. **Improved health utility per health state:**
   For each health state, patients treated with elosulfase alfa would have higher utility values than those on standard care. The utility values are based on the EQ-5D data collected during the period of the MAA for the ERT-Naïve patients. Since no untreated patients were followed-up in the period of the MAA, utility values for Natural History were based on the EQ-5D baseline assessment and the utility values for elosulfase alfa from the last follow-up assessment collected (section 10.1.9).

   Although direct EQ-5D questionnaires were applied to patients, this general tools is not sensitive to capture the utility increment from 6MWT and FVC observed in the patients treated with elosulfase alfa, therefore as a strong positive correlation between patient's 6MWT and FVC with their HRQoL, as measured by the EQ-5D were observed (Lampe et al., 2014), an additional utility value was applied, following the same method presented and approved during the HST2 appraisal:

   - As reported by Lampe et al 2014, for every 10 metres gained in the 6 MWT there was a 0.02 increase in utility. Thereby, indicating that improvement in 6MWT and FVC seen with elosulfase alfa would translate into improved quality of life.

   - The utility for each health state for elosulfase alfa treated patients is increased in accordance to the difference in the clinical outcomes (6MWT or FVC) between elosulfase alfa treated patients and standard care treatment.

4. **Stabilisation of disease progression:**
   Given the cost of elosulfase alfa, it is unlikely that patients would remain on the drug if their disease continues to progress at the same rate as it

was progressing prior to treatment. Hence, BioMarin has assumed that patients whose progression rate is not reduced would discontinue treatment. These patients have been termed ‘non-responders’.

Experiences from other MPS disorders such as MPS VI suggests that treatment with elosulfase alfa would lead to a halting of disease progression in majority of patients. In a 10-year follow-up study of 117 Maroteaux-Lamy syndrome (MPS VI) patients, patients treated with galsulfase for a duration of 7.3 years had maintained a statistically significant increase in FVC (29.3%) and 6MWT (21.1%) over their baseline function and also showed no further degradation of cardiac function (Giugliani et al., 2014).

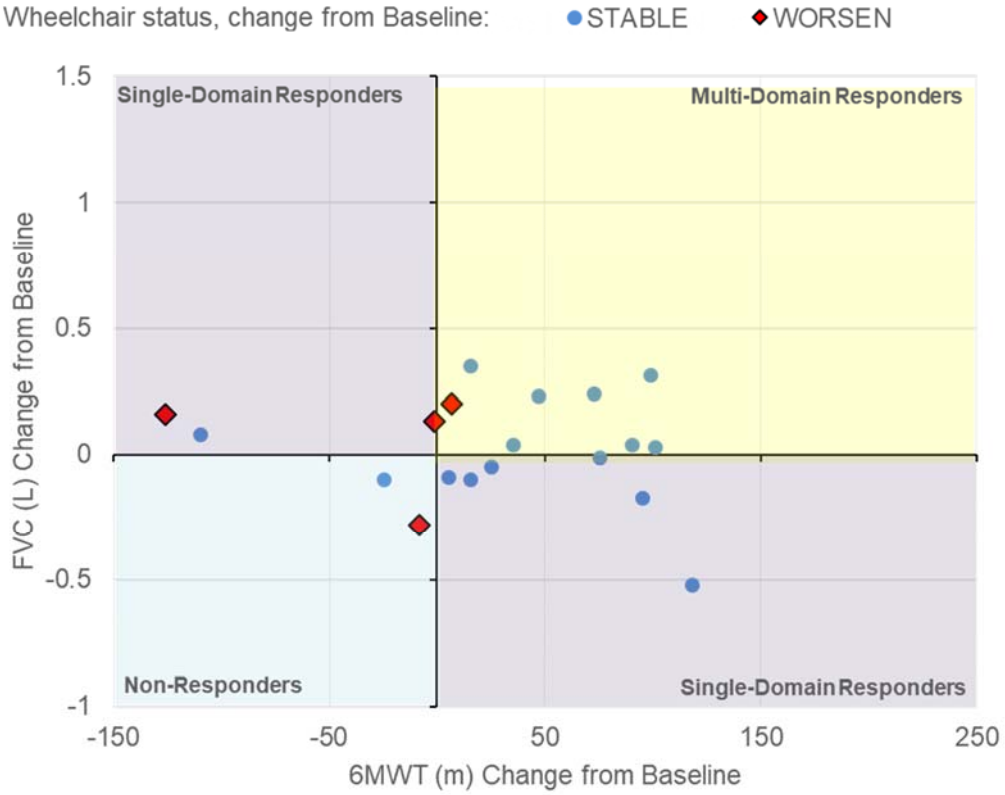
In the first submission in 2015, the model assumes that after initial improvement due to treatment, there would be three groups of patients which would define the rate of long-term progression:

- *Multi-domain responders*: subjects with positive change from baseline in endurance (as measured by 6MWT or 3MSCT) and lung function (as measured by MVV or FVC) during the MOR-005 study.
- *Single domain responders*: subject with positive change from baseline in either endurance (6MWT or 3MSCT) or lung function (MVV or FVC) only, during the MOR-005 study
- *Non-responders*: subject with positive change from baseline in none of 6MWT, 3MSCT, and (MVV or FVC) during the MOR-005 study.

However, based on the long-term outcomes (up to 10 years) observed in the MAA clinical results, the multi-domain criteria proved not be an appropriated method to reflect the long-term dynamic of those patients as changes in either endurance and pulmonary function would not properly reflect the Wheelchair change, as observed in Figure 60 and Figure 61.

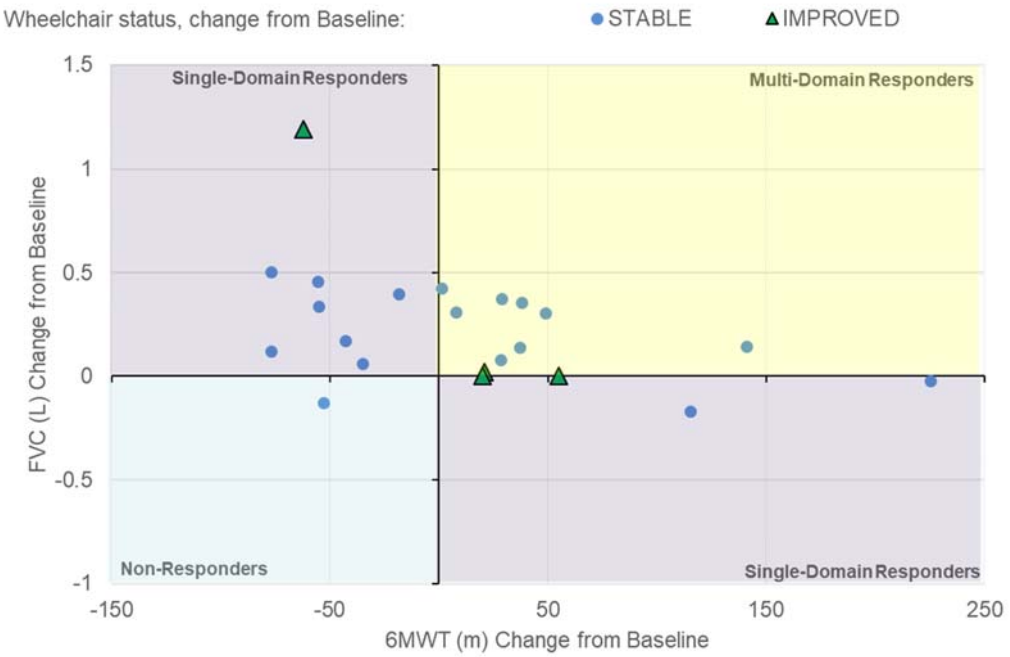
Based on the long-term findings from the MAA, an alternative concept is proposed, which would be based on the long-term Wheelchair change and which is described in Item 12.2.2.

Figure 60. FVC change from baseline compared to 6MWT change from baseline and Wheelchair change. ERT Naïve patient, n=19



Only patients with baseline and follow-up assessment were included in the analysis. Multi-domain responders and single-domain responders are defined as the first submission (HST2 appraisal) and abovementioned.

Figure 61. FVC change from baseline compared to 6MWT change from baseline and Wheelchair change. Ex-Trial patients, n=22



Only patients with baseline and follow-up assessment were included in the analysis. Multi-domain responders and single-domain responders are defined as the first submission (HST2 appraisal) and abovementioned.

5. Delay in surgery and faster recovery rates:

Evidence from the MOR-004/005 clinical studies showed that treatment with elosulfase alfa led to a 4-month delay in time to surgery. As such the costs and outcomes of the surgery, including the utility decrement are adjusted proportionally to reflect this delay.

Based on clinical opinion, treatment with elosulfase alfa would result in faster recovery rates compared to untreated patients (Table 86). This is due to the improved health of elosulfase alfa treated patients at the time of surgery compared to untreated patients.

Table 86. Duration and utility decrement of recovery period following surgery

Surgery	Utility Decrement[a]	Recovery Period (months)	
		Standard Care	Elosulfase + Standard care
Cervical fusion surgery	0.250	6	4
Genus Valgum	0.250	6	4
Spinal decompression	0.250	6	4
Hip surgery	0.250	6	4

Lower spine surgery	0.250	6	4
Aortic Valve replacement	0.010	6	4
Tonsillectomy	0.005	2	1
Ear Tube Placement	0.005	2	1
Corneal Replacement	0.005	2	1
Cataract Surgery	0.005	2	1

a Based on UK expert clinical opinion

Transition probabilities

Transition probabilities are based on change in wheelchair use (for first cycle only), and decline in 6MWT and FVC (subsequent cycles) (Table 87).

Table 87. Transition Probabilities

Natural History Patients (1st cycle only)

Natural History Patients (1st cycle only)	Asympto-matic	No a wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End stage	Death from End Stage Only
Asymptomatic	0.717	0.283	0.000	0.000	0.000	0.000	0.000
No wheelchair use	0.000	0.790	0.210	0.000	0.000	0.000	0.000
Sometimes use wheelchair	0.000	0.030	0.730	0.240	0.000	0.000	0.000
Wheelchair dependent	0.000	0.000	0.170	0.830	0.000	0.000	0.000
Paraplegic	0.000	0.000	0.000	0.000	1.000	0.000	0.000
Predeath	0.000	0.000	0.000	0.000	0.000	1.000	0.000

Natural History Patients (subsequent cycles)

Natural History Patients (subsequent cycles)	Asympto-matic	No a wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only
Asymptomatic	0.717	0.283	0.000	0.000	0.000	0.000	0.000
No wheelchair use	0.000	0.918	0.082	0.000	0.000	0.000	0.000
Sometimes use wheelchair	0.000	0.000	0.949	0.051	0.000	0.000	0.000
Wheelchair dependent	0.000	0.000	0.000	0.867	0.000	0.133	0.000
Paraplegic	0.000	0.000	0.000	0.000	0.867	0.133	0.000
Predeath	0.000	0.000	0.000	0.000	0.000	0.607	0.393

Elosulfase Alfa treated patients (1st cycle only)

Elosulfase Alfa treated patients (1st cycle only)	Asympto-matic	No wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only
Asymptomatic	1.000	0.000	0.000	0.000	0.000	0.000	0.000

No wheelchair use	0.000	0.750	0.250	0.000	0.000	0.000	0.000
Sometimes use wheelchair	0.000	0.150	0.760	0.090	0.000	0.000	0.000
Wheelchair dependent	0.000	0.000	0.540	0.460	0.000	0.000	0.000
Paraplegic	0.000	0.000	0.000	0.000	1.000	0.000	0.000
Predeath	0.000	0.000	0.000	0.000	0.000	1.000	0.000

Elosulfase Alfa treated patients (Long-term stabiliser 2nd cycle onwards)

Elosulfase Alfa treated patients (Long-term stabiliser 2nd cycle onwards)	Asympto-matic	No wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only
Asymptomatic	0.913	0.087	0.000	0.000	0.000	0.000	0.000
No wheelchair use	0.000	1.000	0.000	0.000	0.000	0.000	0.000
Sometimes use wheelchair	0.000	0.000	1.000	0.000	0.000	0.000	0.000
Wheelchair dependent	0.000	0.000	0.000	1.000	0.000	0.000	0.000
Paraplegic	0.000	0.000	0.000	0.000	1.000	0.000	0.000
Predeath	0.000	0.000	0.000	0.000	0.000	0.607	0.393

Elosulfase Alfa treated patients (Mild decliner 2nd cycle onwards)

Elosulfase Alfa treated patients (mild decliner 2nd cycle onwards)	Asympto-matic	No wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only
Asymptomatic	0.913	0.087	0.000	0.000	0.000	0.000	0.000
No wheelchair us	0.000	0.975	0.025	0.000	0.000	0.000	0.000
Sometimes use wheelchair	0.000	0.000	0.984	0.016	0.000	0.000	0.000
Wheelchair dependent	0.000	0.000	0.000	0.958	0.000	0.042	0.000
Paraplegic	0.000	0.000	0.000	0.000	0.958	0.042	0.000
Predeath	0.000	0.000	0.000	0.000	0.000	0.607	0.393

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Patients were assumed to continue to accrue the costs and outcomes of each health state throughout the period of time they remain in that health state. No additional assumptions were made.

The MAA dataset provided a long-term view of the clinical outcomes of patients treated with elosulfase alfa for up to 10 years (Ex-trial patients, see section 9.6.1.2.1). Extrapolations were based mainly on the observed data from the patients in the MAA dataset. Patients treated for a mean treatment

duration of 8.0 years (up to 10 years) are stable or improving in the Wheelchair Change, as of two patients improved the Wheelchair Status from ‘Some use’ to ‘No use’ and two patients improved from Wheelchair Dependent to ‘Some use’, comparing Wheelchair status at MAA enrolment versus last follow-up (**Figure 62**).

Figure 62. Ex-trial Patients dynamic chart: Boxed number represent number of patients moving across the Wheelchair status from the MAA enrolment date versus Last Follow-up.

The Wheelchair change results in the Ex-trial Patients sustain the long-term stability assumption of treated patients over untreated patients (**Figure 63**) and it is translated in the in the economic model as a proportion of patients achieving long-term stability (aka., ‘Long-term stabilizer’) or mild decline (aka., ‘Mild decliner’) after the initial 2 year cycle (Table 88).

Figure 63. Patients showing stability, decline, or improvement in wheelchair status over time versus baseline (based on MPS-HAQ Mobility Q33 and Q33a regarding wheelchair se)

Table 88. Proportion of patients treated with elosulfase alfa achieving long-term stability in Subsequent Years after the two initial cycles

	Asymptomatic	No wheelchair use	Some wheelchair use	Wheelchair dependent	End stage
Long-term stabiliser	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Mild decliner	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

In sensitivity analysis, FVC decrease was linked to reduced mortality risk (please refer to section 12.2.1 above).

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events were not included in the cost-consequence analysis as the only drug-related AEs experienced were infusion reactions. These were managed by infusion rate adjustments and/or treatment with steroids and analgesics. It was assumed, therefore, that these would be included within, and covered by, the cost of administration.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or

estimated clinical model parameter and inputs used in the analysis.

Clinical expert advisers assessed the applicability of the available or estimated clinical model parameters and inputs through the means of expert panel discussion and questionnaire sessions, in accordance with the Delphi technique. The process was conducted in December 2013.

The objectives, methodology, participants and responses in this process are still valid for this submission.

The questions asked

The following questions were put to the participants:

Disease progression

- Average age that patients start to show significant symptoms such as skeletal abnormalities. From the 2 questionnaires, a consensus was reached that patients start to show significant skeletal symptoms at the age of 5.
- Effect of treatment on the development of symptoms. At the meeting, consensus was reached that treatment would delay symptoms by 5 years.
- Average age in each health state
  During the expert panel meeting a consensus was reached on the following ages:

  - Never use wheelchair- 8
  - Sometimes use wheelchair -12
  - Always use wheelchair 16.
- FVC decline After the question was reworded in the second questionnaire, 100% of respondents agreed with the assumption that FVC declines by 0.2L a year.
- FVC Predeath threshold An assumption was made that threshold for movement into the end-stage health state is 0.3L as this is the FVC where mechanical ventilation is required for other diseases such as Duschene's muscular dystrophy. During the Expert panel meeting, there was

consensus agreement on 0.3 L to be the threshold for movement into the predeath health state.

- Time in Always use wheelchair health state before moving to end-stage state. Baseline data from the MorCAP showed that the average FVC for always use wheelchair patients was 1.0 litre. Based on a hypothesized annual decrease of 0.2 litres in FVC and a transition to the predeath state of all patients with FVC ≤ 0.3 L, patients will spend on average 3.5 years in the always wheelchair health state before moving to the end-stage state. A consensus was reached that` patients would spend 7 years in this health state.
- Time in end-stage health state The assumption made was that patients would spend 2 years in predeath health state based of the average age of death being 24.5 years. In Questionnaire 2, 100% agreed with the assumption of 2 years.
- Would you expect patients who are paraplegic due to surgery complications to progress into the "end-stage" state at the same rate as patients that are in the "Always use a wheelchair" state?" In questionnaire 2, all respondents agreed that this would be dependent on which health state they entered the paraplegic health state from.

Surgeries

Before the Delphi panel, the assumptions around surgeries were that tonsillectomy, ear tube placement, corneal replacement and cataract surgery would occur in the asymptomatic health state. Cervical fusion, genus valgum and lower spinal surgery take place in the never use wheelchair health state. Surgeries that take place in sometimes use wheelchair state were assumed to be cervical fusion, genus valgum and hip surgery. It was assumed that in the always use wheelchair state patients will undertake aortic surgery and hip surgery.

From the 2 questionnaires and the expert panel meeting, it was concluded that surgeries would take place as follows:

- Tonsillectomy will take place in the asymptomatic health state

- Ear tube placement surgery will take place in the asymptomatic health state
- Genus Valgum surgery will take place in the never use wheelchair health state
- Lower spine surgery will take place in the never use wheelchair health state
- Hip surgery will take place in the sometimes use wheelchair health state
- Cervical fusion surgery will take place in the sometimes use wheelchair health state
- Spinal decompression surgery will take place in the sometimes use wheelchair health state
- Aortic valve surgery will take place in the always use wheelchair health state
- Corneal replacement surgery will take place in the always use wheelchair health state
- Cataract surgery will take place in the always use wheelchair health state

Cervical fusion surgery Before the Delphi process the assumption was that 37.5% of patients would undergo cervical fusion surgery in the sometimes use wheelchair health state and 37.5% will undergo in never use wheelchair health state. In the both questionnaires, 80% of respondents agreed with this assumption. From the expert panel meeting it was decided that this surgery will take place in the sometimes use a wheelchair state only

Risk of complications which would result in patients becoming paraplegic
The assumption made before the Delphi process was that there was a 10% risk of paraplegia from cervical fusion therapy. In both questionnaire 60% of respondents agreed with this assumption. There was a suggestion from clinicians that 10% was too high; however, at the expert panel meeting consensus was reached at a 10% risk.

Proportion of patients undergoing each surgery Clinicians were asked what proportion of patients they would expect to undergo each surgery.

At the expert panel meeting all clinicians felt that the above figure represented the proportion of patients undergoing each surgery. The final proportions were decided as follows:

- Tonsillectomy – 43%
- Ear tube placement surgery– 30%
- Genus Valgum – 31%
- Hip surgery– 32%
- Spinal decompression surgery– 40%
- Aortic surgery –15%
- Corneal replacement surgery – 3%
- Cataract Surgery – 3%
- Cervical fusion surgery – Sometimes 37.5%, Symptomatic 37.5%

The expert panel meeting also concluded that the proportion of patients requiring tonsillectomy and ear tube placement may decrease with treatment but all other surgeries will only be delayed (no effect of proportion).

Risk of death due to surgery Before the Delphi process, it was assumed that there is a 12% risk of death for surgeries in the "Never use wheelchair", "Sometimes use wheelchair" and "Always use wheelchair“ health states and no risk of death in surgeries in the asymptomatic health state. In Questionnaire 1, 20% of respondents agreed with this assumption and 80% disagreed. Some clinicians comments that there would still be a risk of death in asymptomatic health state and the estimate was quite high for current patients. This was changed to be an open question in the second questionnaire.

The agreed risk of death for each surgery following the expert panel meeting is shown in

Table 89 below.

Table 89. Agreed risk of death for each surgery following consensus meeting

Surgery	Health State	Risk of death
Tonsillectomy	Asymptomatic	2.3%
Eartube placement surgery	Asymptomatic	2.1%
Corneal replacement surgery	Asymptomatic	2.1%
Cataract Surgery	Asymptomatic	2.1%
Genus valgum surgery	Never Use Wheelchair	4.6%
Lower spine surgery	Never Use Wheelchair	6.4%
Genus valgum surgery	Sometimes Use Wheelchair	5.8%
Hip surgery	Sometimes Use Wheelchair	5.8%
Spinal decompression surgery	Sometimes Use Wheelchair	10.2%
Aortic valve surgery	Always Use Wheelchair	16%
Hip surgery	Always Use Wheelchair	13.4%

Recovery from surgery

In Questionnaire 1 it was asked whether there would be a recovery period after surgery where patients would have a lower quality of life. All respondent agreed that there would be. Therefore, in Questionnaire 2 the question was changed to be an open question and participants were asked for the expected recovery time for each surgery.

The results from questionnaire 2 were that patients will spend 3 weeks in the recovery period following tonsillectomy, cataract surgery and lower spine surgery, 2 weeks in the recovery period following ear tube placement surgery and 3.4 weeks in the recovery period from corneal replacement surgery. It was also agreed that patients will spend 16 weeks in the recovery period following genus valgum surgery, 24.4 weeks in the recovery period following spinal decompression surgery and 22.2 weeks following aortic valve surgery In the expert panel meeting clinicians felt that that this question should be answered by surgeons to get a more accurate idea of the length of time spent in recovery.

In the second questionnaire, participants were asked to give the percentage decrease in quality of life that they would expect to see in patients in this recovery period following surgery. Means calculated for the answers given in the questionnaire are as shown in Table 90. These values were agreed to be representative of the expected decrease in quality of life in the recovery period following surgery.

Table 90. Expected percentage decrease in quality of life in recovery period

Surgery	Percentage decrease in quality of life (%)
tonsillectomy	18.75
eartube placement	18.33
corneal replacement	21.67
cataract	18.33
lower spine	55.00
genus valgum	41.25
spinal decompression	65.00
aortic valve	58.75
hip surgery	51.25

In questionnaire 1, it was asked whether participants would expect elosulfase alfa to shorten the time that patients spend this this recovery period. 40% of respondent answer that they would expect treatment to shorten the recovery period and 60% disagreed. In questionnaire 2, this was changed to an open question where participants were asked to state how much they would expect treatment to shorten recovery time. Respondents gave very varied answers to this question and at the expert panel meeting clinicians stated that surgeons should be asked in order to get a more accurate idea of the expected length of time spent in recovery.

Mortality

Mortality in the model is calculated from data from a clinical trial for ERT treatment in MPS VI patients. The results from this trial showed that untreated patients had a 10-year mortality risk of 60% while treated patients had a mortality risk of 19.48%. In Questionnaire 1 40% of respondents agreed that MPSVI would show similar mortality to MPS IVA, 60% disagreed this. Clinicians who did not agree felt that they would expect MPS IVA to have a

higher mortality due to overall more extra skeletal burden. The results from Questionnaire 2 were similar to those in question 1.

In the expert panel meeting it was agreed that the mortality would be as follows:

- 52% of patients go through the whole model
- 12% die due to surgery
- 12% die due to trauma
- 12% die due to pulmonary
- 12% die due to cardiology

In questionnaire 2 it was asked whether it is expected that elosulfase alfa treatment for MPS IVA would to have a similar effect on reducing mortality as ERT treatment has on MPS VI patients. In Questionnaire 1, 60% said that would expect a similar effect and 40% said they would not expect a similar effect. Participants suggested that they would expect a lower effect because overall more extra-skeletal disease burden in MPS VI, which is more amenable to ERT. The same result came from the second questionnaire. In the expert panel meeting it was agreed that treatment would have no effect on mortality related to trauma and surgery but would have an effect on mortality related to cardiology and pulmonary complications.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

Table 91. Summary of variables applied in the cost-effectiveness model

Variable	Value	Range or 95% CI (distribution)	Source
Clinical variables			
Average weight			
• Asymptomatic	12.3kg	11.1kg-13.4kg (Mor-CAP data ±10%)	Mor-CAP data
• No wheelchair	21.36 kg	19.07kg – 23.65kg (normal)	MAA Dataset (November 2019)
• Sometimes wheelchair	22.24 kg	20.23 kg – 24.23kg (normal)	MAA Dataset (November 2019)
• Always wheelchair	44.93 kg	41.72 kg – 48.11kg (normal)	MAA Dataset (November 2019)
Yearly decline in 6MWT	*6.84m*	5.25m-8.75m (normal)	
Yearly decline in FVC	*0.1L*	0.075L-0.125L (normal)	
Utilities			
Treated patients			
Asymptomatic health state utility	1.000	varied by ±10% (beta distribution)	
No wheelchair use utility	0.780	varied by ±10% (beta distribution)	
Sometimes use wheelchair utility	0.682	varied by ±10% (beta distribution)	
Wheelchair dependent utility	0.166	varied by ±10% (beta distribution)	
Paraplegic health state utility	0.166	varied by ±10% (beta distribution)	
End stage health state utility	0.024	varied by ±10% (beta distribution)	
Untreated patients			
Asymptomatic health state utility	1.000	varied by ±10% (beta distribution)	
No wheelchair use utility	0.468	varied by ±10% (beta distribution)	
Sometimes use wheelchair utility	0.368	varied by ±10% (beta distribution)	

Wheelchair dependent utility	0.080	varied by ±10% (beta distribution)	
Paraplegic health state utility	0.057	varied by ±10% (beta distribution)	
End stage health state utility	0.024	varied by ±10% (beta distribution)	
Other			
Delay in Surgery	0.3 years	0.333 years-0.367 years (normal)	
Delay in becoming symptomatic with treatment	5 years	3 years-10 years (normal)	Clinical assumption
Wheelchair shift proportions		Beta/Dirichlet	
Discount Rates for costs and QALYS	1.5% for both costs and health effects	0%-6%	NICE Guide to Methods of Technology Appraisal 2013
Utility benefit associated with home care	0.00	0.00-0.05	Clinical Assumption
Costs			
Price of the technology per treatment/patient	£750 per 5mg vial	All costs were varied by ±10%	BNF, 2014.
Cost of treatment administration	£207	All costs were varied by ±10%	Based on the cost of Vascular Access except for Renal Replacement Therapy without CC (PbR tariff 2013-2014)
Resource use costs			

GP	£33.70	All costs were varied by ±10%	PSSRU 2019; average of GP consultation (with/without direct care staff costs and with/without qualifications)
Nurse	£6.07	All costs were varied by ±10%	PSSRU 2019, nurse (GP) cost per hour is £40 and assuming 9.22 mins per consulation, same as GP
Accident and emergency	£156.00	All costs were varied by ±10%	NHS Reference Costs 2018/2019 average of all A&E costs
Pulmonary complication specialist	£157.00	All costs were varied by ±10%	NHS Reference Costs 2018/2019 Respiratory medicines Outpatient appointment
Pain management specialist	£650.00	All costs were varied by ±10%	NHS reference cost 2011-12. Consultant led: Follow up attendance Non-admitted face to face – 241 paediatric pain
Mental Health specialist	£282.00	All costs were varied by ±10%	NHS Reference Costs 2018/2019 Children and Adolescent Mental Health Services, Outpatient Attendances
Cardiology specialist visit	£139.00	All costs were varied by ±10%	NHS Reference Costs 2018/2019 Cardiology Outpatient appointment
Ophthalmology	£98.00	All costs were varied by ±10%	NHS Reference Costs 2018/2019 Ophthalmology Outpatient appointment
ENT specialist	£107.00	All costs were varied by ±10%	NHS Reference Costs 2018/2019 ENT Outpatient appointment
Ventilation	£3,071.00	All costs were varied by ±10%	NHS Reference Costs 2018/2019: PK72C Paediatric Metabolic Disorders with CC Score 0 (using ICD10 E762 + OPCS E851)
Cervical Fusion Operation	£20,029	All costs were varied by ±10%	NHS Reference Costs 2018/2019 HC51E and HC51D - Complex Instrumented Correction of Spinal Deformity, 18 years and under, with CC Score 3+ and 0-2; average taken of bot
Genus Valgum surgery	£4,203	All costs were varied by ±10%	NHS Reference Costs 2018/2019 Intermediate Knee Procedures for Trauma (<18, >18; CC Score 0,1,2+): HRGs - HT24A,HT24B,HT24C,HT24D
Spinal decompression surgery	£13,631	All costs were varied by ±10%	Uplifted 2006 cost to 2020 (using https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator)
Hip surgery	£6,040	All costs were varied by ±10%	NHS Reference Costs 2018/2019 - HN12F Very Major Hip Procedures for Non-Trauma with CC Score 0-1 (using ICD10 codes E762 + OPCS code W371)
Lower spine surgery	£13,631	All costs were varied by ±10%	Assumed same as spinal decompression
Aortic valve replacement	£7,908	All costs were varied by ±10%	NHS Reference Costs 2018/2019 - EC13C Major Procedures for Congenital Heart Disease with CC Score 0-3 (using ICD10 codes E762+ I352 + OPCS codes K261+Y794)

Tonsillectomy	£1,913	All costs were varied by ±10%	NHS Reference Costs 2018/2019: CA60C Tonsillectomy 4 years and over (using ICD10 E762 + OPCS F341)
Ear tube placement	£1,211	All costs were varied by ±10%	NHS Reference Costs 2018/2019: CA35B Insertion of Grommets, between 2 and 18 years (using OPCS D151 and ICD10 E762)
Corneal replacement.	£3,035	All costs were varied by ±10%	NHS Reference Costs 2018/2019: BZ61B Complex, Cornea or Sclera Procedures, with CC Score 0-1 (using OPCS C464 and ICD10 E762)
Cataract surgery	£2,581	All costs were varied by ±10%	NHS Reference Costs 2018/2019: BZ32B Intermediate, Cataract or Lens Procedures, with CC Score 0-1 (using OPCS C751 and ICD10 E762)

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The cost consequence model follows the recommended clinical management of MPS IVA patients as per the UK SOP (2014 Lysosomal Storage Disorders Expert Group). Standard costs are presented in

Table 91 (item 12.2.6).

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Resource data was not included in the systematic review. Delphi panel results and the UK SOP for management of MPS IVA patients provided a clear reference to patient management and resource requirements. These have been tabulated in Table 92 below.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[11].

Clinical expert advisers assessed the applicability of the resources used in the model through the means of expert panel discussion and questionnaire sessions, in accordance with the Delphi technique. The process was conducted in December 2013 for the first submission (HST2 appraisal) and is still valid for the current submission.

Questions asked

The participants were asked the following:

Healthcare professional use

GP visits. In questionnaire 1, the participants were asked how many times patients would need to visit a physician for pain management and for pulmonary complications. In questionnaire 2, this was changed to ask for the number of GP visits a year per patient for each health state.

[11] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

What would be the expected number of visits per patient per year for each health state to:

- A nurse
- A specialist for pulmonary complications
- A specialist for pain management
- A specialist for mental health. This question was only asked in the second questionnaire. It was brought up because of comments in the first questionnaire.
- A specialist for cardiology complications. This question was only asked in the second questionnaire. It was brought up because of comments in the first questionnaire.
- An ear, nose and throat (ENT) specialist. This question was only asked in the second questionnaire. It was brought up because of comments in the first questionnaire.
- An ophthalmologist. This question was only asked in the second questionnaire. It was brought up because of comments in the first questionnaire.

Hospitalisations

It can be concluded from the 2 questionnaires that the amount of times that patients require planned hospitalisations will increase as the disease progresses. The length of stay would also increase as the disease progresses so patients who are in the always use wheelchair state will require more visits to hospital the those never in a wheelchair or sometimes in a wheelchair and these visits would lest for longer.

Accident and Emergency

Clinicians were asked the expected number of visits to accident and emergency per year for each health state.

Other resources

A further suggestion from clinicians in the questionnaires and the expert panel meeting were that hearing aids are needed by all MPS IVA patients.

Treatment effect on resource use

In questionnaire 2, the participants were asked “How would you expect treatment to affect the amount of GP, consultant and nurse resources needed in each health state?”

20% said treatment would not affect GP resources used, 60% said that it would decrease resources use, 20% said it would increase the resources used. In the expert panel meeting it was discussed that GP resources would decrease because patients will be seeing consultants more regularly whilst they are on treatment and so are likely to just discuss problems with them. It was suggested that visits are not a proxy of health state.

20% said that treatment would decrease the consultant resources used, 80% said that treatment would increase the resources used. Comments included that ERT requires more frequent monitoring. In the expert panel meeting it was discussed that consultant resources will increase with treatment does to increased monitoring.

20% said treatment would not affect the number of nurse visits, 20% said it would decrease nurse visits, 60% said it would increase nurse visits. In the expert panel meeting it was discussed that this was dependent on the type of nurse. Nurse visits would increase with treatment as the nurse would be required to administer the treatment. However, the number of visits to nurses would decrease as patients would see the nurses at the hospital instead[12].

A&E visits

[12] It is important to note that homecare provison was not discussed during the Delphi process or at the expert panel meeting. As noted elsewhere, once stabilised on therapy, it is anticipated that MPS IVA patients would receive elosulfase alfa at home.

How would you expect treatment to affect the number of A&E visits needed in each health state? 80% said treatment would decrease the number of A&E visits. In the expert panel meeting, consensus was reached that A&E visits would decrease with treatment.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The approved list price given in the British National Formulary is £750.00 per vial.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification

Not applicable. The list price is used in the model.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Table 92. Costs per treatment/patient associated with the technology in the cost- effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	£750 per 5mg vial	BNF, 2020.
Administration cost	£207	Based on the cost of Vascular Access except for Renal Replacement Therapy without CC (PbR tariff 2013-2014)

The costs of elosulfase alfa consist of two components: drug costs and administration costs. For each patient, elosulfase alfa drug costs would vary depending on the weight of the patient. To consider of the heterogeneity of the disease, an average weight was assigned to each health state based on natural history data from the MAA dataset (Table 91).

The cost of elosulfase alfa is estimated as £750 for a 5mg vial which is the list price.

For simplicity, BioMarin assumed that any remaining drug after infusion would be discarded. Therefore, the number of 5mg vials needed to administer a dose is rounded up to the nearest whole number.

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

MPS IVA patients suffer many symptoms over their lifetime which would require the consumption of healthcare resources. The type of health care resources utilised depends on patient's health state. For each health state, the resources utilised were sourced from expert panel of physicians experienced

in the management of MPS IVA (Table 93). The unit costs are presented in Table 94.

Table 93. List of health states and associated costs in the cost- effectiveness model

Resource	Visits per cycle					
	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent	Paraplegic	End Stage
Non-Hospital						
Visit to GP	1.2	1.8	1.8	2.5	2.9	0.0
GP Nurse visit	0.7	0.9	1.4	1.8	2.3	0.0
Hospitalisation						
Accident & Emergency Visit	0.0	0.0	0.0	0.3	0.3	0.0
Pulmonary Complication Visits	0.1	0.4	0.7	1.1	1.3	0.0
Pain Management Specialist Visits	0.1	0.4	0.7	1.1	1.3	0.0
Mental Health Specialist Visits	0.0	0.2	0.4	0.7	1.0	0.0
Cardiology Specialist Visits	0.0	0.2	0.4	0.7	1.0	0.0
Ophthalmology	0.4	0.6	0.6	0.6	0.6	0.0
ENT Specialist Visits	0.6	0.9	0.8	1.1	1.0	0.0
Other						
Ventilation*	0.0	0.0	0.0	0.0	0.0	1.0

Unit costs of resources and surgeries were obtained from a variety of data sources including the NHS reference costs 2018-2019, literature sources, and the PPSRU unit costs of health and social care 2019 manual (Table 94).

Table 94. Unit costs of healthcare resources and surgeries

Resource	Cost	Source
GP	£33.70	PSSRU 2019; average of GP consultation (with/without direct care staff costs and with/without qualifications)
Nurse	£6.07	PSSRU 2019, nurse (GP) cost per hour is £40 and assuming 9.22 mins per consulation, same as GP
Accident and emergency	£156.00	NHS Reference Costs 2018/2019 average of all A&E costs
Pulmonary complication specialist	£157.00	NHS Reference Costs 2018/2019 Respiratory medicines Outpatient appointment
Pain management specialist	£650.00	NHS reference cost 2011-12. Consultant led: Follow up attendance Non-admitted face to face – 241 paediatric pain
Mental Health specialist	£282.00	NHS Reference Costs 2018/2019 Children and Adolescent Mental Health Services, Outpatient Attendances
Cardiology specialist visit	£139.00	NHS Reference Costs 2018/2019 Cardiology Outpatient appointment
Ophthalmology	£98.00	NHS Reference Costs 2018/2019 Ophthalmology Outpatient appointment
ENT specialist	£107.00	NHS Reference Costs 2018/2019 ENT Outpatient appointment
Ventilation	£3,071.00	NHS Reference Costs 2018/2019: PK72C Paediatric Metabolic Disorders with CC Score 0 (using ICD10 E762 + OPCS E851)
Cervical Fusion Operation	£20,029	NHS Reference Costs 2018/2019 HC51E and HC51D - Complex Instrumented Correction of Spinal Deformity, 18 years and under, with CC Score 3+ and 0-2; average taken of bot
Genus Valgum surgery	£4,203	NHS Reference Costs 2018/2019 Intermediate Knee Procedures for Trauma (<18, >18; CC Score 0,1,2+): HRGs - HT24A,HT24B,HT24C,HT24D
Spinal decompression surgery	£13,631	Uplifted 2006 cost to 2020 (using https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator)
Hip surgery	£6,040	NHS Reference Costs 2018/2019 - HN12F Very Major Hip Procedures for Non-Trauma with CC Score 0-1 (using ICD10 codes E762 + OPCS code W371)
Lower spine surgery	£13,631	Assumed same as spinal decompression
Aortic valve replacement	£7,908	NHS Reference Costs 2018/2019 - EC13C Major Procedures for Congenital Heart Disease with CC Score 0-3 (using ICD10 codes E762+ I352 + OPCS codes K261+Y794)
Tonsillectomy	£1,913	NHS Reference Costs 2018/2019: CA60C Tonsillectomy 4 years and over (using ICD10 E762 + OPCS F341)

Ear tube placement	£1,211	NHS Reference Costs 2018/2019: CA35B Insertion of Grommets, between 2 and 18 years (using OPCS D151 and ICD10 E762)
Corneal replacement.	£3,035	NHS Reference Costs 2018/2019: BZ61B Complex, Cornea or Sclera Procedures, with CC Score 0-1 (using OPCS C464 and ICD10 E762)
Cataract surgery	£2,581	NHS Reference Costs 2018/2019: BZ32B Intermediate, Cataract or Lens Procedures, with CC Score 0-1 (using OPCS C751 and ICD10 E762)

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Not applicable. Adverse events were not included in the cost-consequence analysis.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Home care therapy

To reflect the standard practice in England, whereby most patients have home infusions of ERT with or without the supervision of a nurse, BioMarin has assumed that 90% of MPS IVA patients would have home infusions following an initial 3-month period of receiving their infusion in a hospital (outpatient) setting. This assumption is based on evidence from the Gaucher's Disease Association which shows about 90% of patients having home infusions (Gaucher's Disease Association). The remaining 10% of patients were assumed to carry on undertaking hospital infusions. The cost of elosulfase alfa was discounted by 20% for patients who receive home infusion due to the VAT waiver for home infusion drugs. In addition to reflect the additional convenience, reduced stress and discomfort to patients and their caregivers,

patients with home infusions were assigned an additional utility benefit of 0.02. This assumption is based on evidence from other LSDs such as Fabry disease and Hunter syndrome which have shown improvements in quality of life once patients are switched to home care therapy (Ceravolo et al., 2013, Di Vito R et al., 2013).

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

There are no additional cost savings of which we are aware, however, as understanding on the treatment will continue to increase other cost savings may become apparent.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Yes, the uncertainty has been investigated as per the probabilistic sensitivity analysis described below in sections 12.5.11 below

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Yes, scenario-based deterministic and probability sensitivity analyses were undertaken. The variables used, together with the range of the variation (Upper and lower values) and the method used are summarised in Tables 95-97 below.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table 95. Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Value	Lower Bound	Upper Bound	Method for upper and lower bounds
Average weight per health state	Asymptomatic – 12.3 kg No use – 23.3 kg Sometimes – 27.6kg Always –27.3 kg	Asymptomatic – 11.1 kg No use – 21.05 kg Sometimes – 25.58kg Always – 24.05kg	Asymptomatic – 13.4 kg No use – 25.63 kg Sometimes – 29.57 kg Always- 30.46 kg	95% confidence intervals from MorCap except asymptomatic (±10%)
Annual decline in 6MWT	6.84 m	5.25 m	8.75 m	±25%
Annual decline in FVC	0.1 L	0.075 L	0.125 L	±25%
Utilities	All utilities were varied by ±10%			
Costs	All costs varied by ±10%			
Delay in Surgery	0.3 years	0.333 years	0.367 years	±10%
Delay in becoming symptomatic with treatment	5 years	3 years	10 years	Based on clinical assumptions
Discount Rates for costs and QALYS	1.5% for both costs and health effects	0%	6%	NICE Guide to Methods of Technology Appraisal 2013
Utility benefit	0.00	0.00	0.05	Assumptions

associated with home care				

Table 96. Variables used in multi-way scenario-based sensitivity analysis

Variable	Delay in symptom development due to elosulfase alfa treatment of asymptomatic patients	Progression rate of mild decliner compared to treatment untreated patients
Base case	5 years	50%
Optimistic scenario	7 years	30%
Conservative scenario	2 years	70%

Table 97. Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution
Average weight per health state	Asymptomatic – 12.3 kg No use – 23.3 kg Sometimes – 27.6kg Always –27.3 kg	Normal
Annual decline in 6MWT		Normal
Annual decline in FVC		Normal
Utilities		Beta
Costs		Normal
Delay in Surgery		Normal
Delay in becoming symptomatic with treatment		Normal
Wheelchair shift proportions		Beta/Dirichlet

In addition, the following additional scenario analysis were modelled:

1. Proportion of long-stabiliser patients changing to 95% and mild decliner to 5%.
2. Proportion of long-stabiliser patients changing to 90% and mild decliner to 10%.
3. Utility values including patients who underwent surgery at last follow-up

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Not applicable. All parameters were included in either scenario-based or probabilistic sensitivity analyses.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

12.5.1 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The clinical outcomes in the model are modelled as an extrapolation of the observed clinical results in both the MAA dataset results and the MOR-001 natural history data results. As such there is no comparison between the model and the clinical results

12.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 98. Proportion of cohort in each health state

Elosulfase Alfa	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent	Paraplegic	Advanced stage	Death
baseline							
5 years							
10 year							
25 years							
50 years							
100 years							
Standard Care	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent	Paraplegic	Advanced stage	Death
baseline							
5 years							
10 year							
25 years							
50 years							
100 years							

12.5.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used

to demonstrate QALYs accrued in each health state over time.

Table 99. QALYs accrued per health state in the model – elosulfase alfa-treated patients

Elosulfase ALFA	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent	Paraplegic	Advanced stage	Surgery	Caregiver disutility
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 100. QALYs accrued per health state in the model – standard care

Standard of Care	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent	Paraplegic	Advanced stage	Surgery	Caregiver disutility
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.5.4 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Not applicable.

12.5.5 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table 101. Summary of QALY gain by health state (discounted)

Health state	QALY Elosulfase alfa	QALY no treatment	Absolute increment	% absolute increment
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]%
No use	[redacted]	[redacted]	[redacted]	[redacted]%
Sometimes	[redacted]	[redacted]	[redacted]	[redacted]%
Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]%
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]%
End-stage	[redacted]	[redacted]	[redacted]	[redacted]%
Surgery	[redacted]	[redacted]	[redacted]	[redacted]%
Carer Burden	[redacted]	[redacted]	[redacted]	[redacted]%
Total	[redacted]	[redacted]	[redacted]	**100%**

12.5.6 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Base-case results

In the base case scenario, MPS IVA patients receiving standard medical care (no treatment) generated [redacted] Life Years and [redacted] QALYs during their lifetime. If treated with elosulfase alfa as an add-on therapy, these numbers increased to [redacted] life years and [redacted] QALYs, resulting in health gains of [redacted] Life Years and [redacted] QALYs, respectively (Table 102). Not treating MPS IVA patients with elosulfase alfa resulted, on average, in a cost of £[redacted] over a patient's lifetime.

Treatment with elosulfase alfa resulted in a mean lifetime costs of £[redacted], a difference of £[redacted] (Table 103). The incremental cost per QALY for patients treated with elosufalse alfa is £[redacted].

Table 102. Base case results: undiscounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	28.71	7.31	38.02	33.69
Elosulfase alfa	66.73	41.00		

Table 103. Base case results: undiscounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

When the 1.5% discount rate was applied to the effects, patients with MPS IVA who received standard medical care were estimated to have gained [redacted] life years and [redacted] QALYs. Patients treated with elosulfase alfa plus best supportive care accrued [redacted] life years and [redacted] QALYs. This resulted in an incremental difference [redacted] life years, and [redacted] QALYs gained. Table 104 presents the discounted incremental and total effects considered in the model.

Table 104. Base case results: discounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa	[redacted]	[redacted]		

When discounted, treatment with elosulfase alfa resulted in a mean lifetime costs of £[redacted], while untreated patients resulted in a mean lifetime cost of £[redacted], a difference of £[redacted]. The incremental cost per QALY for patients treated with elosufalse alfa is £[redacted] (Table 105).

Table 105. Base case results: discounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

12.5.7 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

Table 106. Summary of costs by category of cost per patient (discounted)

Item	Cost Elosulfase alfa	Cost No Treatment	Absolute increment	% absolute increment
Elosulfase Alfa	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Administration	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Wheelchairs	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Surgery	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Asymptomatic	£[redacted]	£[redacted]	£[redacted]	[redacted]%
No use	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Sometimes	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Wheelchair dependent	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Paraplegic	£[redacted]	£[redacted]	£[redacted]	[redacted]%
End-stage	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Caregiver	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Indirect Costs	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Total	£[redacted]	£[redacted]	£[redacted]	**100.0%**

12.5.8 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Table 107. Summary of costs by health state per patient

Item	Cost Elosulfase alfa	Cost No Treatment	Absolute increment	% absolute increment
Asymptomatic	£[redacted]	£[redacted]	£[redacted]	[redacted]%
No use	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Sometimes	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Wheelchair dependent	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Paraplegic	£[redacted]	£[redacted]	£[redacted]	[redacted]%
End-stage	£[redacted]	£[redacted]	£[redacted]	[redacted]%

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not Applicable.

Sensitivity analysis results

12.5.10 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

The one-way sensitivity analysis shows that the most important parameters in the model affecting the modelled outcomes at the discount rate used for costs and the QALYs. The change in the annual decline in the 6MWT values, utility values and average body weight per health state all had very minimal impact on the outcomes. Table D32 shows the lower and upper range considered in the analysis.

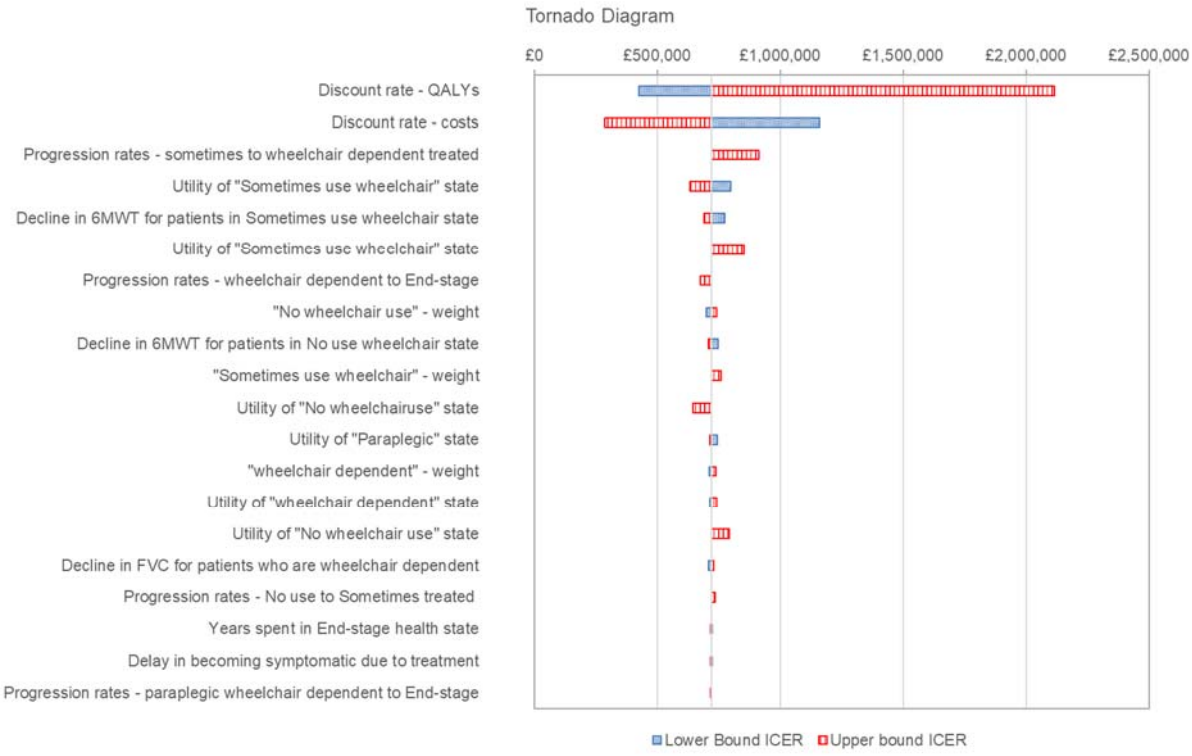
For pragmatism and ease of explanation of the impact of costs and outcomes as QALYs, a Tornado diagram is also presented in Figure 64. Overall, with the exclusion of the discount rate, the impact of varying each parameter would be relatively less influential on the results (see Table 108 and Figure 64).

Table 108. One-way sensitivity analysis of most important parameters

Variable	Base Case Value	Lower/ Upper Range	
		Lower Case Value	Upper Case Value
Asymptomatic Weight	12.3 Kg	9.9 Kg	14.7 Kg
No wheelchair use weight	21.4 Kg	19.1 Kg	23.7 Kg
Sometimes use weight	22.2 Kg	20.2 Kg	24.2 Kg
Wheelchair dependent weight	44.9 Kg	41.7 Kg	48.1 Kg
Annual decline in 6MWT (No wheelchair use)	6.8 meters	4.0 meters	10.0 meters
Annual decline in 6MWT (Sometimes use wheelchair)	6.8 meters	4.0 meters	10.0 meters
Annual decline in FVC (Wheelchair dependent)	0.100 L	0.050 L	0.200 L
Annual decline in FVC (Paraplegic)	0.100 L	0.050 L	0.200 L
Untreated: Asymptomatic health state utility	1	0.88	0.97
Untreated: No wheelchair use utility	0.468	0.750	0.880
Untreated: Sometimes use wheelchair utility	0.368	0.480	0.640
Untreated: Wheelchair dependent utility	0.080	0.050	0.200
Untreated: Paraplegic health state utility	0.057	0.050	0.200
Untreated: End stage health state utility	0.024	0.010	0.050
Treated: Asymptomatic health state utility	1.000	0.880	0.970
Treated: No wheelchair use utility	0.733	0.880	0.970
Treated: Sometimes use wheelchair utility	0.697	0.600	0.800
Treated: Wheelchair dependent utility	0.166	0.050	0.200
Treated: Paraplegic health state utility	0.166	0.050	0.200
Discount rate - costs	1.5%	0.0%	6.0%

Discount rate - QALYs and LYs	1.5%	0.0%	6.0%
Delay in becoming asymptomatic due to elosulfase alfa treatment	5 years	2 years	7 years
Years spent in End-stage health state	2 years	1 years	3 years
Progression rates of Responders - in relation to Natural History			
Long-term stabiliser: No wheelchair use	0%	0%	10%
Long-term stabiliser: Sometimes use wheelchair	0%	0%	10%
Long-term stabiliser: Wheelchair dependent	0%	0%	10%
Long-term stabiliser: Wheelchair dependent paraplegic	0%	0%	10%
Mild decliner: No wheelchair use	50%	30%	70%
Mild decliner: Sometimes use wheelchair	50%	30%	70%
Mild decliner: Wheelchair dependent	50%	30%	70%
Mild decliner: Wheelchair dependent paraplegic	50%	30%	70%

Figure 64. Tornado diagram showing the results of one-way sensitivity analysis results for the main model parameters.



12.5.11 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

The undiscounted and discounted results from the scenario analyses, as presented in the Item 12.5.6 with life years gained and QALYs as the primary clinical outcomes are reported below in Tables 109-120:

Table 109. Scenario 1 (Proportion of long-stabiliser patients changing to 95% and mild decliner to 5%): undiscounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	28.71	7.31	36.97	32.42
Elosulfase alfa	65.69	39.74		

Table 110. Scenario 1 (Proportion of long-stabiliser patients changing to 95% and mild decliner to 5%): undiscounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

Table 111. Scenario 1 (Proportion of long-stabiliser patients changing to 95% and mild decliner to 5%): discounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa	[redacted]	[redacted]		

Table 112. Scenario 1 (Proportion of long-stabiliser patients changing to 95% and mild decliner to 5%): discounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

Table 113. Scenario 2 (Proportion of long-stabiliser patients changing to 90% and mild decliner to 10%): undiscounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]

Elosulfase alfa	[redacted]	[redacted]		

Table 114. Scenario 2 (Proportion of long-stabiliser patients changing to 90% and mild decliner to 10%): undiscounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

Table 115. Scenario 2 (Proportion of long-stabiliser patients changing to 90% and mild decliner to 10%): discounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa	[redacted]	[redacted]		

Table 116. Scenario 2 (Proportion of long-stabiliser patients changing to 90% and mild decliner to 10%): discounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

Table 117. Scenario 3 (Utility values including patients who underwent surgery at last follow-up) undiscounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa	[redacted]	[redacted]		

Table 118. Scenario 3 (Utility values including patients who underwent surgery at last follow-up): undiscounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

Table 119. Scenario 3 (Utility values including patients who underwent surgery at last follow-up): discounted

	Life Years	QALYS	Incremental Life Years	Incremental QALYs
Standard treatment	[redacted]	[redacted]	[redacted]	[redacted]
Elosulfase alfa	[redacted]	[redacted]		

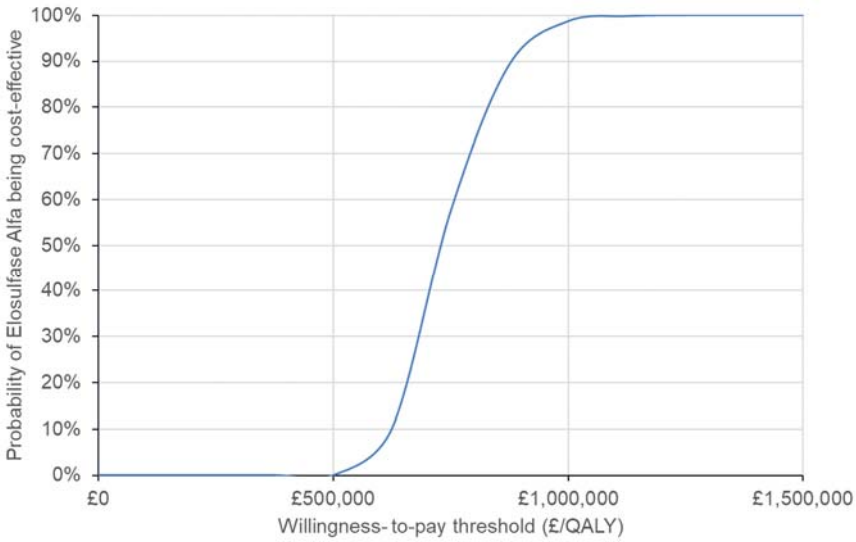
Table 120. Scenario 3 (Utility values including patients who underwent surgery at last follow-up): discounted

	Cost	Incremental cost	ICER
Standard treatment	£[redacted]	£[redacted]	£[redacted]
Elosulfase alfa	£[redacted]		

12.5.12 Present results of the probabilistic sensitivity analysis described in table D10.3.

Figure 65 shows the cost-effectiveness acceptability of elosulfase alfa against standard medical care before discounting, after Monte Carlo simulation of all model parameters and for different willingness to pay values per QALY. The probability of elosulfase alfa treatment being cost-effective at WTP values of about £[redacted], £[redacted], £[redacted] per QALY were [redacted], [redacted] and [redacted] respectively.

Figure 65. Elosulfase alfa against standard medical therapy after Monte Carlo simulation of all model parameters. Cost-effectiveness acceptability curve.



12.5.13 What were the main findings of each of the sensitivity analyses?

The one directional sensitivity analysis has been discussed in Section 12.5.11 and shows that the model is most sensitive to discount rates, utilities for the no wheelchair and some wheelchair health state utilities.

Additional two scenarios are proposed to assess the impact of alternative proportion of treated patients achieving long-term stabilization. As presented in item 12.2.2, after initial years of treatment patients treated with elosulfase alfa for up to 10 years in the MAA dataset tend to stabilize in the Wheelchair Status, which is the main long-term assumption for the base case.

In scenarios 1 and 2 we proposed to assess different proportion of patients achieving long-term stabilization based on the number of patients who failed to treatment or decide to discontinue from the MAA. According to the latest data-cut ([redacted]),[redacted]% of patients discontinued or fail to meet the MAA criteria (Table 121), and based on this findings, the Scenario 1 is defined as 5% of patients not achieving long-term stabilization (i.e., 5% of patients as mild decliner) and Scenario 2 is defined as 10% of patients not achieving long-term stabilization (I.e., 10% of patients as mild decliner).

Table 121. Number of patients who discontinued treatment during the MAA

Total number of patients enrolled in the MAA†	Patients who discontinued or fail the MAA criteria	
	Number of patients §	As a percentage of total enrolled patients in the MAA
[redacted]	[redacted]	[redacted]%

†Excluding 1 patient with duplicated records.
§ Patients: GOS003; UCLH008; UCLH011; UCLH013 and CMFT001. A sixth patient stopped treatment because moved to a new country and was not considered as a discontinuation or fail.

An additional scenario 3 is also proposed to assess the impact of the exclusion of patients who underwent surgery in the utility score calculation, as patient disposition provided in item 10.1.9. Only one patient ([redacted]) was excluded from the base case analysis, as a knee surgery was reported as an important event happening close to the last follow-up assessment. This patient ([redacted]) reported at a baseline EQ-5D utility score of [redacted], a score of [redacted] in the first year and a score of [redacted] in the second year (last follow-up available).

Results of the sensitivity analysis are summarized below in Table 122.

Table 122. Summary of sensitivity analyses (Discounted)

Scenarios	Description	Incremental QALY	ICER
Base case	Current base based in the MAA results as presented in this submission	[redacted]	£[redacted]
Scenario 1	Proportion of long-term stabiliser patients changing to 95% and mild decliner to 5%	[redacted]	£[redacted]
Scenario 2	Proportion of long-term stabiliser patients changing to 90% and mild decliner to 10%	[redacted]	£[redacted]
Scenario 3	Utility values including patients who underwent surgery at last follow-up	[redacted]	£[redacted]

12.5.14 What are the key drivers of the cost results?

The key driver for reducing cost results is a slower diseases progression and as such a reduction in the number of patients moving to costly wheelchair dependent health states. Patients treated over up to 10 years demonstrated

stable result in change of wheelchair status hence reducing the life-time cost by maintaining patients in a less wheelchair dependent health state.

Miscellaneous results

12.5.15 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

Not Applicable.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not Applicable.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not Applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Not Applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not Applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The economic model submitted in this appraisal was already submitted and validated by The NICE Committee in the HST2 appraisal. The new assumptions based on MAA results generated a comparable incremental QALYs to first model hence the real-world long-term results reiterate the original assumption presented in the first appraisal.

Additionally, BioMarin compared the life expectancy (life years gained) and causes of death in the model against the natural history patients from a published UK mortality study for MPS IVA patients (Lavery and Hendriksz, 2015). The mean age at death in the model was 29.51 years compared to 25.30 from the Lavery and Hendriksz study (30.74 over the last 14 years). The proportion of deaths from the end-stage health state - which can be used as a proxy for deaths from cardio-pulmonary complications and organ failure - was 88% in the BioMarin compared to 89% for the Lavery and Hendriksz study (Lavery and Hendriksz, 2015). These findings, which were also validated by UK clinical experts consulted by BioMarin, confirm the validity of the BioMarin analysis.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No economic studies or papers were identified during the systematic review of the literature.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes, the analysis is relevant to all groups of MPS IVA patients and services that could potentially benefit from the technology in accordance with the marketing authorisation.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Mortality is mainly driven by the end-stage health state, where all patients are assumed to die after 2 years. Hence the gains in life years associated with elosulfase-treated patients versus standard care patients are mainly driven by fewer patients getting to the end-stage health state due to the assumption of stabilisation or reduction in disease progression for elosulfase alfa -treated patients. In addition, stabilisation of disease progression means patients stay in higher utility states for longer due to their improved quality of life.

The assumption of disease stabilisation in majority of patients is supported by the evidence collected during the MAA, which show patients with up to 10 years of treatment are stable in the wheelchair status, which means no worsening is observed after the initial years of treatments, as presented in details in item 12.2.2.

This economic model updated with the data collected during the period of the MAA confirm that the treatment with elosulfase alfa brings clear and important clinical benefits, resulting in an improvement in survival and quality of life for patients.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Additional evidence from a large cohort of patients from MARS study should enhance the understanding of the long-term benefit of treatment with elosulfase alfa in the next years. Although, it is still soon to assess the benefit in survival resulted from the treatment with elosulfase alfa a similar reduction in mortality rates observed in other MPS disorders is anticipated to MPS VIA resulted from the long-term treatment with elosulfase alfa. Further research in the area is needed.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

BioMarin has calculated that four new MPS IVA patients in England would be eligible for treatment per year. This is an estimation based in the actual number of new patients observed during period of the MAA.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

For the purposes of calculating the overall budget impact presented in section 13.7, BioMarin has assumed:

- All newly diagnosed MPS IVA patients would receive elosulfase alfa treatment;
- After the initial 3 years of treatment, a drop-out of one patient per year is anticipated;
- A compliance rate of 95% per year is assumed across all patients;
- The average weight of 25.2 kg per patient is considered to calculate the acquisition cost of elosulfase alfa. The average weight is based on the patients enrolled in the MAA (see Item 12.1.4).

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

BioMarin is not aware of any such costs associated with treatment over and above those already incurred in clinical practice for MPS diseases.

13.4 Describe any estimates of resource savings associated with the use of the technology.

The disaggregated budget impact calculation in section 13.7 below identifies potential reduction in the number of surgical interventions, caregiver costs and wheelchair use/dependency, based in the findings from the economic analysis.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

BioMarin is not aware of any other opportunities of cost saving.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

It is anticipated that savings could accrue to the welfare, education and local government budgets. Further details are given in section 14.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Two scenarios are presented in Table 123 below: one where elosulfase alfa treatment is funded and made available to eligible patients and a second scenario where elosulfase alfa is not funded or made available to NHS patients.

Table 123. Estimated budget impact for the NHS and PSS

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Elosulfase Alfa Treated Population	4.0	8.0	12.0	15.0	17.0
Elosulfase Alfa: Acquisition cost	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Elosulfase Alfa: Acquisition cost and administration	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Total cost: elosulfase alfa available	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Total cost: elosulfase alfa not available	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Net Budget Impact	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]

The disaggregated costs showing net budget impact are given in Tables 124-128 below.

Table 124. Estimated budget impact for the NHS and PSS – disaggregated cost by year

	Year 1		
	Elosulfase alfa available	Elosulfase alfa not available	Net Budget Impact
Elosulfase Alfa	£[redacted]		£[redacted]
Administration	£[redacted]		£[redacted]
Wheelchairs	£[redacted]	£[redacted]	£[redacted]
Surgery	£[redacted]	£[redacted]	£[redacted]
Asymptomatic	£[redacted]	£[redacted]	£[redacted]
No use	£[redacted]	£[redacted]	£[redacted]
Sometimes	£[redacted]	£[redacted]	£[redacted]
Wheelchair dependent	£[redacted]	£[redacted]	£[redacted]
Paraplegic	£[redacted]	£[redacted]	£[redacted]
End-stage	£[redacted]	£[redacted]	£[redacted]
Caregiver	£[redacted]	£[redacted]	£[redacted]
Total	£[redacted]	£[redacted]	£[redacted]

Table 125. Estimated budget impact for the NHS and PSS – disaggregated cost by year

Year 2

	Elosulfase alfa available	Elosulfase alfa not available	Net Budget Impact
Elosulfase Alfa	£[redacted]		£[redacted]
Administration	£[redacted]		£[redacted]
Wheelchairs	£[redacted]	£[redacted]	£[redacted]
Surgery	£[redacted]	£[redacted]	£[redacted]
Asymptomatic	£[redacted]	£[redacted]	£[redacted]
No use	£[redacted]	£[redacted]	£[redacted]
Sometimes	£[redacted]	£[redacted]	£[redacted]
Wheelchair dependent	£[redacted]	£[redacted]	£[redacted]
Paraplegic	£[redacted]	£[redacted]	£[redacted]
End-stage	£[redacted]	£[redacted]	£[redacted]
Caregiver	£[redacted]	£[redacted]	£[redacted]
Total	£[redacted]	£[redacted]	£[redacted]

Table 126. Estimated budget impact for the NHS and PSS – disaggregated cost by year

	Year 3		
	Elosulfase alfa available	Elosulfase alfa not available	Net Budget Impact
Elosulfase Alfa	£[redacted]		£[redacted]
Administration	£[redacted]		£[redacted]
Wheelchairs	£[redacted]	£[redacted]	£[redacted]
Surgery	£[redacted]	£[redacted]	£[redacted]
Asymptomatic	£[redacted]	£[redacted]	£[redacted]
No use	£[redacted]	£[redacted]	£[redacted]
Sometimes	£[redacted]	£[redacted]	£[redacted]
Wheelchair dependent	£[redacted]	£[redacted]	£[redacted]
Paraplegic	£[redacted]	£[redacted]	£[redacted]
End-stage	£[redacted]	£[redacted]	£[redacted]
Caregiver	£[redacted]	£[redacted]	£[redacted]
Total	£[redacted]	£[redacted]	£[redacted]

Table 127. Estimated budget impact for the NHS and PSS – disaggregated cost by year

	Year 4		
	Elosulfase alfa available	Elosulfase alfa not available	Net Budget Impact
Elosulfase Alfa	£[redacted]		£[redacted]
Administration	£[redacted]		£[redacted]
Wheelchairs	£[redacted]	£[redacted]	£[redacted]

Surgery	£[redacted]	£[redacted]	£[redacted]
Asymptomatic	£[redacted]	£[redacted]	£[redacted]
No use	£[redacted]	£[redacted]	£[redacted]
Sometimes	£[redacted]	£[redacted]	£[redacted]
Wheelchair dependent	£[redacted]	£[redacted]	£[redacted]
Paraplegic	£[redacted]	£[redacted]	£[redacted]
End-stage	£[redacted]	£[redacted]	£[redacted]
Caregiver	£[redacted]	£[redacted]	£[redacted]
Total	£[redacted]	£[redacted]	£[redacted]

Table 128. Estimated budget impact for the NHS and PSS – disaggregated cost by year

	Year 5		
	Elosulfase alfa available	Elosulfase alfa not available	Net Budget Impact
Elosulfase Alfa	£[redacted]		£[redacted]
Administration	£[redacted]		£[redacted]
Wheelchairs	£[redacted]	£[redacted]	£[redacted]
Surgery	£[redacted]	£[redacted]	£[redacted]
Asymptomatic	£[redacted]	£[redacted]	£[redacted]
No use	£[redacted]	£[redacted]	£[redacted]
Sometimes	£[redacted]	£[redacted]	£[redacted]
Wheelchair dependent	£[redacted]	£[redacted]	£[redacted]
Paraplegic	£[redacted]	£[redacted]	£[redacted]
End-stage	£[redacted]	£[redacted]	£[redacted]
Caregiver	£[redacted]	£[redacted]	£[redacted]
Total	£[redacted]	£[redacted]	£[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

BioMarin considers the budget impact analysis to be robust. The number of the incidence estimates can be calculated with a degree of certainty.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services or are associated with significant benefits other than health.

Patients with MPS IVA are highly functioning individuals, with the capacity and capability to achieve in both education and employment. However, the natural history of MPS IVA disease, and the significant functional and other impairments caused by the progression of disease, means that patients are frequently forced to reduce their level of activity, education or employment – or to cease altogether – by the time they reach their mid to late-20s.

In addition, having an MPS IVA patient in the family can adversely impact on the education and/or employment status of siblings and parents/caregivers. Parents of MPS IVA patients often adapt their working lives and other social activities around the physical and mental health of their child; some have to

stop work altogether, particularly when the MPS IVA patient is nearing the end of his or her life. Further details about the impact on caregivers are given in the burden of illness study (Hendriksz 2014d) described in item 7.2 and in item 14.4 below.

By reducing or delaying disease progression in patients with MPS IVA, therefore, and based upon the expert opinion of treating clinicians in the UK, it is reasonable to anticipate that treatment with elosulfase alfa could result in:

- Better physical and mental health and improved quality of life for caregivers;
- Greater likelihood of caregivers remaining in full- or part-time employment for a longer period of time;
- Improved lives for siblings of patients with MPS IVA – with less disruption to their own education, less time spent on caregiving
- Better socialisation for patients, their caregivers and families.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It is anticipated that treatment with elosulfase alfa could result in cost savings to the following three government departments or budgets:

- Education budget – a child with MPS IVA will receive a statement of special educational needs, which will usually involve the cost of classroom assistance and adaptations to the fabric of the school (for example, to widen spaces to accommodate a wheelchair). These costs may be reduced, or postponed, if the patient derives clinical benefit from treatment with elosulfase alfa.
- Local Government budget – cost savings may accrue (in terms of reduced Disabled Facilities Grant payments, for example) if fewer adaptations need to be made to a patient's home, or if the adaptations needed are less costly.

- Welfare budget – the more independent and capable of ADLs the patient is, the less dependent they – or their caregivers - are on respite care, or on disability and other welfare payments. If the patient and/or their caregiver is able to remain in employment, savings to the welfare budget will accrue (for example, it is reasonable to assume a reduction in benefit payments if a patient is able to remain in employment due to slower or delayed disease progression), and HM Treasury benefits from payments of income tax.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Patients with MPS IVA experience constant challenges in life as regards mobility, pain, fatigue and an environment that is poorly adapted to their needs (Lavery 2014b). Consequently, the costs to the patient and their families which are not reimbursed by the NHS are considerable. Because of the extreme short stature typically manifested by patients with MPS IVA, together with the unique physical structure of patients with the disease, a large number of ordinary everyday objects need to be adapted for use, all at the cost of the patient/family.

These include:

- Adaptation of home and car
- Specialist bespoke clothes and shoes – it is difficult to find adult-appropriate clothing in children's sizes "off-the-shelf"
- Cost of specialist lightweight electric wheelchairs – although the NHS funds the cost of a standard manual wheelchair to the value of £500, these are completely inadequate and unsuitable for a patient with MPS

In addition, patients and their families incur substantial extra financial costs in terms of:

- Travel costs to and from frequent hospital appointments, hospital car parking charges, and/or travel to and from specialist school

- Additional time off work, particularly for adult patients and the primary caregivers of paediatric patients
- Additional support from carers and specialist childminders
- Excess payments to “top-up” Disabled Facilities Grant payments whre the grant is insufficient to meet the full cost of the adaptations needed
- Private extra tuition - special assistance with schooling and adaptation for work
- The cost of physiotherapy and hydrotherapy sessions to relieve pain and address some of the symptoms of disease

In terms of non-financial “costs”, there is some evidence to suggest that the parents and siblings of patients with MPS IVA under-achieve in their careers, as a consequence of caring for someone with MPS IVA, time taken off work, and so on.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

An international survey was performed to evaluate the global burden among primary caregivers of patients with MPS IVA. Collected outcomes included self-reported time spent on caregiving, the proportion of daily activities (derived from the Mucopolysaccharidosis Health Assessment Questionnaire (MPS HAQ)) requiring caregiver assistance, and how the patient’s age and wheelchair use affect both of these. In addition, the survey evaluated the impact of caregiving on the caregivers’ relationship with family and friends, physical and mental health, their employment status and income. The study methodology and results have been published (Hendriksz 2014c; Hendriksz 2014d).

The study was a voluntary, single-assessment, cross-sectional, paper-based survey administered in person or by mail via local staff members of advocacy and patient support groups and/or physicians and clinics.

A total of 56 caregivers from 5 different countries (Brazil, Colombia, Germany, Spain and Turkey) completed the survey. Most caregivers (82.1%) were mothers of patients with MPS IVA, with a mean age of 42.6 years (age range 16-71). 52 parents (92.9%) considered themselves as the primary caregiver, although most indicated that they were satisfied or very satisfied with the level of support they received from their partner.

Two-thirds of the parents (N=37) cared for children with MPS IVA ≤17 years and one-third (N=19) for adult patients 18 years or older.

The study showed that adult patients who always used a wheelchair required substantially more caregiving time than patients who were more mobile. This was less apparent in children.

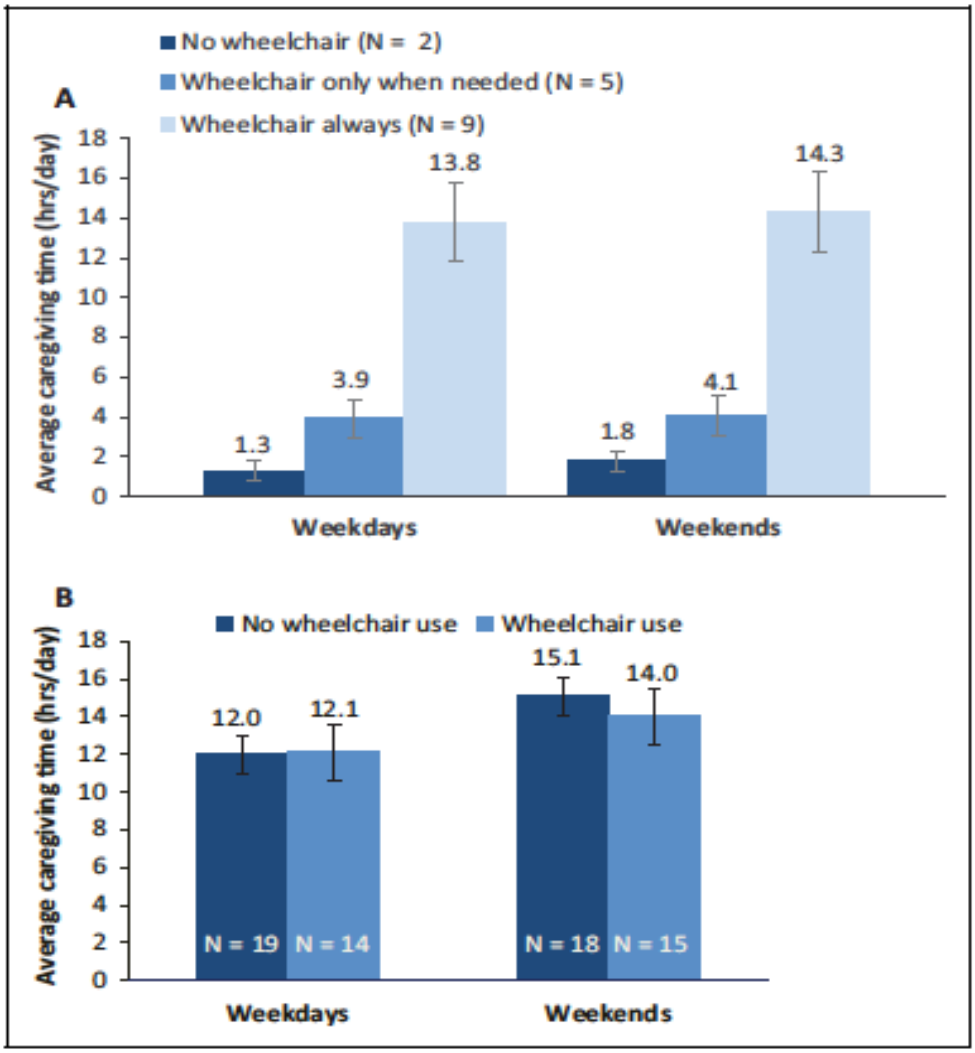
Of the 17 adult patients for whom wheelchair information was available, 2 never used a wheelchair, 6 used it only when needed, and 9 used it always. Of the 37 children with MPS IVA syndrome, 22 never used a wheelchair, 14 used it only when needed, and 1 used it always.

Wheelchair use increased with age. There were significant differences in mean age between patients not using a wheelchair (9.96 years) and those using a wheelchair sometimes (16.48 years, $P < 0.001$) or all the time (20.15 years, $P < 0.001$).

In adults, patients who always used a wheelchair required more care time than the other patients. Indeed, 13.8 hours and14.3 hours a day of care were given to an adult who always used a wheelchair on weekdays and weekends, respectively, while this time was only 3.9 hours on weekdays and 4.1 hours on weekend days when the wheelchair was used only when needed (Figure 66, Part A). The amount of caregiver time was 1.3 hours on weekdays and 1.8 hours on weekend days for those adult patients who did not use a wheelchair.

For children, the number of caregiving hours was not affected by wheelchair use (Figure 66, part B). Caregivers of 2 patients spent more time caregiving than those of 1 patient. However, this difference was not statistically significant.

Figure 66. Mean number of caregiving hours/day on weekdays and weekends for adults (A) and children (B) with MPS IVA according to wheelchair use/mobility level



The broader impact and burden of MPS IVA disease on caregivers (that is, beyond the time spent in caregiving) has already been described in section 9 and 10).

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The establishment of the Morquio A Registry Study (MARS) and the data collect over the period of the MAA represents a significant development for strengthening the evidence base in this disease area. The registry was

designed from the outset with input from expert UK clinicians and is an innovative and collaborative model for research into rare diseases.

In addition to MARS, BioMarin is sponsoring the following ongoing research initiatives:

- Work on diagnostics and improved analytics
- Outcomes studies in countries and ISTs across all MPS diseases are ongoing in, for example, Turkey, the UK and the USA.
- Prospective PRO studies are also in progress.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

BioMarin envisages that the clinical development programme for elosulfase alfa and its subsequent reimbursement and use in the NHS could still help position the UK as an attractive environment within which to undertake rare disease research and focus investment, as well as add significantly to the level of understanding about the epidemiology and management of rare MPS diseases. The programme to date represents a world-leading collaboration between clinicians and patient advocacy organisations, with the majority of clinical expertise and experience now being concentrated in the UK.

Importantly,

- The high-risk, ‘first in man’ studies for elosulfase alfa (MOR-002) were performed exclusively in centres in the UK.
- 7 of the 8 clinical trial centres were located in the UK and have demonstrated their capabilities as centres of excellence in the management of rare MPS diseases. Amongst other things, these centres provide information on where study numbers have increased and the level of research funding in the metabolic CSG.
- The largest clinical cohort of patients, who participated in the pivotal MOR-004 study, were UK patients.

- The clinical programmes being run in some centres have won awards for their contribution to improved diagnosis and disease awareness, and a better understanding of the disease; for example, the MOR100 programme at Great Ormond Street Hospital.

- The research programme includes the first study to include homecare, as well as a study focussed exclusively on paediatric patients.

- The MARS registry will integrate natural history data, clinical and other outcomes for the first time,

BioMarin has made a substantial investment and commitment to life sciences and to patients in the UK. This investment and commitment is ongoing through a number of clinical and scientific research programmes across the whole BioMarin development and product portfolio, and in a number of rare diseases, including other MPS diseases. All of these clinical trials involved UK sites; in many cases, the Primary Investigator is based in the UK.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

The Morquio A Registry Study (MARS), as per the post-marketing authorisation commitments given to the European Medicines Agency, will continue to collect evidence on patients with MPS IVA until 2025. Therefore, MARS should be the main source of clinical effectiveness in the next 5 years.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

The primary mechanism for reviewing the clinical effectiveness of elosulfase alfa will be the MARS registry described in section 14.7 above.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

As noted in section 8.2 above, Birmingham, Cambridge, London and Manchester are all designated national centres for the diagnosis and management of LSDs. These centres are all involved in clinical studies into the treatment and management of mucopolysaccharide diseases - including MPS IVA - and have extensive experience of ERT. These centres all have an ongoing commitment to managing patients in dedicated outpatient and inpatient facilities. Moreover, the geographical distribution of the centres works well for both paediatric and adult MPS IVA patients, facilitating an excellent transition of adolescent patients to adulthood.

In addition, it is important to note that clinicians in the UK have the most experience of using elosulfase alfa as the majority of MOR-004 study participants were treated at study sites in the UK. In addition, the UK has more than 10 years' experience of managing 17 MPS IVA patients in the MOR-100 study and more than 7 years' experience in additional patients in the MOR-005 study.

Because of the level of expertise and experience which already exists in the UK, BioMarin anticipates that only limited, if any, additional training will be required to administer elosulfase alfa. Apart from this, no additional expertise is required to ensure the safe and effective use of the technology and it is expected to fit within existing clinical practice.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No additional infrastructure is required to ensure the safe and effective use of elosulfase alfa in those centres which are already experienced in the diagnosis and management of LSDs

Section F - Managed Access Arrangements

(please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

A new managed access agreement is not proposed in this submission.

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

Not applicable. As stated above.

15.2 Describe the specifics of the MAA proposal, including:

- *The duration of the arrangement, with a rationale*
- *What evidence will be collected to reduce uncertainty*
- *How this evidence will be collected and analysed*
- *The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA*
- *Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)*
- *Funding arrangement, including any commercial proposals or financial risk management plans*
- *The roles and responsibilities of clinical and patient groups during the MAA*
- *What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed*

Not applicable. As stated above.

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

Not applicable. As stated above.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following electronic databases were searched.

- Embase via the Embase.com platform
- Medline via the Embase.com platform
- Medline InProcess and electronic publications ahead-of-print via PubMed
- The Cochrane Library's CDSR and CENTRAL databases via the Cochrane Library
- The Cochrane Library's DARE databases via the Centre for Reviews and Dissemination, University of York (CRD) website (https://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp).

17.1.2 The date on which the search was conducted.

The dates on which the searches were conducted:

11 October 2019 (Embase.com)

11 October 2019 (Pubmed)

11 December 2019 (CDSR, CENTRAL)

18 December 2019 (DARE)

4 November 2020: An updated search was done to find new clinical publications on MPS IVA. The search terms and inclusion/ exclusion criteria were same as the original search of November 2019. The new search generated 84 articles at the 1st pass (EMBASE/ MEDLINE and 11 papers of other note), and 8 articles after the 2nd pass. The summary of these 8 articles is presented in Section **Error! Reference source not found.** below.

17.1.3 The date span of the search.

The date span of the search for utility data:

Embase – Database inception (1974) to date of search

MEDLINE – Database inception (1966) to date of search

Pubmed – Database inception to the day prior to search

CDSR, CENTRAL – Database inception to Issue 10 of 12, October 2019

DARE – Database inception to 31st March 2015 (database closed)

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strings use Emtree Medical Subject Heading (MeSH) terms and broad free-text terms, using a specific method developed and recommended by Wichor Bramer[13], a biomedical information specialist in Erasmus MC, Rotterdam, to create high-quality and thorough searches in Embase.com (Embase and Medline together).

The population terms are bespoke and include a comprehensive set of free text terms and the index term for morquio syndrome.

[13] http://www.slideshare.net/wichor

To identify RCTs in Embase, the Embase RCT search strategy was used, amended to Embase.com format [14]:

'crossover procedure':de OR 'double blind procedure':de OR 'randomized controlled trial':de OR 'single blind procedure':de OR (random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl*) NEAR/1 blind) OR assign* OR allocat* OR volunteer*):de,ab,ti

To identify RCTs in in-process and e-publications ahead of print in PubMed, the Cochrane handbook's Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format, has been used, without rows #9 and #10:

#1	*randomized controlled trial [pt]*
#2	*controlled clinical trial [pt]*
#3	*randomized [tiab]*
#4	*placebo [tiab]*
#5	*clinical trials as topic [mesh: noexp]*
#6	*randomly [tiab]*
#7	*trial [ti]*
#8	*#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7*
#9	*animals [mh] NOT humans [mh]*
#10	*#8 NOT #9*

The search strings employed are given below for Embase and MEDLINE (Table 129), MEDLINE in-process and e-publications ahead-of-print (Table 130) and the Cochrane Library (Table 131).

Embase/medline search string

Platform: Embase.com

14 Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

URL: https://www.elsevier.com/solutions/embase-biomedical-research

Date searched: 11-Oct-2019

Hits: 516

RCT filter: Embase RCT search strategy, amended to Embase.com format [15]

Table 129: Embase and Medline search string

[15] Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

No.	Query	Results
#1	'morquio syndrome'/exp OR morquio*:de,ab,ti OR morqio*:de,ab,ti OR morkio*:de,ab,ti OR brailsford*:de,ab,ti OR keratosulfaturia*:de,ab,ti OR osteochondrodystrophia*:de,ab,ti OR galns*:de,ab,ti OR 'n acetylgalactosamine 6 sulfatase':de,ab,ti OR 'n acetylgalactosamine 6 sulfate':de,ab,ti OR 'n acetyl d galactosamine 6 sulfate 6 sulfohydrolase':de,ab,ti OR 'n acetyl d galactosamine 6 sulphate 6 sulfohydrolase':de,ab,ti OR 'n acetylgalactosamine 6 sulphate sulfatase':de,ab,ti OR mpsiv*:de,ab,ti OR 'mps iv':de,ab,ti OR 'mps iva':de,ab,ti OR 'iv mps':de,ab,ti OR 'iva mps':de,ab,ti OR mps4*:de,ab,ti OR 'mps 4':de,ab,ti OR 'mps 4a':de,ab,ti OR '4 mps':de,ab,ti OR '4a mps':de,ab,ti OR ((('typ? 4' OR 'typ? iv' OR typ?4 OR typ?iv OR 'typ? 4a' OR 'typ? iva' OR typ?4a OR typ?iva) NEAR/5 (mps* OR muco* OR muko*)):de,ab,ti) OR ((typ* NEAR/3 (four OR '4' OR '4a' OR iv OR iva) NEAR/5 (mps* OR muco* OR muko*)):de,ab,ti) OR ((familial NEAR/3 osseous NEAR/3 dystrophy):de,ab,ti) OR ((kerato NEAR/3 sulfaturia):de,ab,ti) OR (((mucopolysaccharidos* OR mucopolysacharidos* OR mukopolysaccharidos*OR 'muco polysaccharidosis' OR 'muco polysaccharidoses') NEAR/7 (four OR '4' OR '4a' OR iv OR iva OR 'typeiv' OR 'type4')):de,ab,ti)	3069
#2	'crossover procedure':de OR 'double blind procedure':de OR 'randomized controlled trial':de OR 'single blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEAR/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR (((doubl* OR singl*) NEAR/1 blind):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2476512
#3	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'case control study'/exp OR 'case study'/exp OR cohort*:de,ab,ti OR (case*:de,ab,ti AND control*:de,ab,ti) OR (case*:de,ab,ti AND series:de,ab,ti)	3864384
#4	nonrandomi$ed:ab,ti OR ‘non randomi$ed’:ab,ti OR (((controlled OR extension) NEAR/3 (trial* OR study OR studies OR phase)):ab,ti)	492932
#5	'register'/exp OR 'disease registry'/exp OR register:ab,ti OR registry:ab,ti	272219
#6	#2 OR #3 OR #4 OR #5	5974188
#7	#1 AND #6	526
#8	'systematic review'/exp OR 'meta analysis'/exp OR 'comparative effectiveness'/exp OR metaanalysis:ab,ti OR 'meta analysis':ab,ti OR 'meta regression':ab,ti OR 'adjusted indirect comparison':ab,ti OR ((systematic* NEAR/3 review*):ab,ti) OR (((mixed OR indirect) NEAR/3 treatment*NEAR/3 comparison*):ab,ti) OR ((simulated NEAR/3 treatment* NEAR/3 comparison*):ab,ti) OR ((match* NEAR/4 adjust* NEAR/3 (indirect OR comparison*)):ab,ti) OR ((comparative NEAR/3 effectiveness):ab,ti) OR ((nma NEAR/3 (network OR metaanalysis OR 'meta analysis')):ab,ti) OR ((itc NEAR/3 (indirect OR treatment* OR comparison*)):ab,ti) OR ((mtc NEAR/3 (mixed OR treatment* OR comparison*)):ab,ti) OR ((maicNEAR/4 (match* OR adjust* OR indirect OR comparison*)):ab,ti) OR ((stc NEAR/3 (simulated OR treatment* OR comparison*)):ab,ti)	466782
#9	#1 AND #8 AND [2018-2019]/py	10

No.	Query	Results
#10	#7 OR #9	531
#11	rat:ti OR rats:ti OR rodent$:ti OR mouse:ti OR mice:ti OR murine:ti OR hamster$:ti	1703811
#12	#10 NOT #11	528
#13	#12 AND ('chapter'/it OR 'conference review'/it OR 'letter'/it)	7
#14	#12 NOT #13	521
#15	'case report':ti	291457
#16	#14 AND #15	5
#17	#14 NOT #16	516

Medline in-process and e-publications ahead of print search string

Platform: Pubmed

URL: https://www.ncbi.nlm.nih.gov/pubmed

Date searched: 11-Oct-2019, and tracked via e-alert until 13-Nov-2019

Hits: 19

RCT filter: Cochrane handbook's Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format, has been used, without rows #9 and #10

Table 130: Medline in-process and e-publications search string

No.	Query	Results
#1	Search ("Mucopolysaccharidosis IV"[mh] OR morquio*[tiab] OR morqio*[tiab] OR morkio*[tiab] OR brailsford*[tiab] OR keratosulfaturia*[tiab] OR osteochondrodystrophia*[tiab] OR GALNS*[tiab] OR “N acetylgalactosamine 6 sulfatase”[tiab] OR “N acetylgalactosamine 6 sulfate”[tiab] OR “n acetyl d galactosamine 6 sulfate 6 sulfohydrolase”[tiab] OR “n acetyl d galactosamine 6 sulphate 6 sulfohydrolase”[tiab] OR “n acetylgalactosamine 6 sulphate sulfatase”[tiab] OR MPSIV*[tiab] OR “MPS IV”[tiab] OR “MPS IVA”[tiab] OR “IV MPS”[tiab] OR “IVA MPS”[tiab] OR MPS4*[tiab] OR “MPS 4”[tiab] OR “MPS 4A”[tiab] OR “4 MPS”[tiab] OR “4A MPS”[tiab] OR ((“typ? 4”[tiab] OR “typ? iv”[tiab] OR typ?4[tiab] OR typ?iv[tiab] OR “typ? 4a”[tiab] OR “typ? iva”[tiab] OR typ?4a[tiab] OR typ?iva[tiab]) AND (MPS*[tiab] OR mucopoly*[tiab] OR muko*[tiab])) OR (type*[tiab] AND (four[tiab] OR “4”[tiab] OR “4A”[tiab] OR IV[tiab] OR IVA[tiab]) AND (MPS*[tiab] OR mucopoly*[tiab] OR muko*[tiab])) OR (familial[tiab] AND osseous[tiab] AND dystrophy[tiab]) OR (kerato[tiab] NEAR/3 sulfaturia[tiab]) OR ((mucopolysaccharidos*[tiab] OR mucopolysacharidos*[tiab] OR mukopolysaccharidos*[tiab] OR “muco polysaccharidosis”[tiab] OR “muco polysaccharidoses”[tiab]) AND (four[tiab] OR “4”[tiab] OR “4A”[tiab] OR IV[tiab] OR IVA[tiab] OR “typeIV”[tiab] OR “type4”[tiab])))	3194
#2	Search "Clinical Trials as Topic"[Mesh:NoExp]	188696
#3	Search (“randomized controlled trial”[pt] OR “controlled clinical trial”[pt])	580502
#4	Search (randomized[tiab] OR randomised[tiab] OR placebo*[tiab] OR randomly[tiab] trial[ti])	145727
#5	Search (“Cohort Studies”[mh] OR “Longitudinal Studies”[mh] OR “Prospective Studies”[mh] OR “Follow-Up Studies”[mh] OR “Case-Control Studies”[mh] OR cohort*[tw] OR ((case[tw] OR cases[tw]) AND (control*[tw] OR series[tw])))	2877757
#6	Search (“non randomized”[tw] OR “non randomised”[tw] OR nonrandomized[tw] OR nonrandomised[tw] OR ((controlled[tw] OR extension[tw]) AND (trial*[tw] OR study[tw] OR studies[tw] OR phase[tw])))	1142793
#7	Search (“registries”[mh] OR register[tiab] OR registry[tiab])	195300
#8	Search (#2 OR #3 OR #4 OR #5 OR #6 OR #7)	3923199
#9	Search (#1 AND #8)	527
#10	Search (“Meta-Analysis”[pt] OR "Network Meta-Analysis"[mh] OR metaanalysis[tiab] OR “meta analysis”[tiab] OR “meta regression”[tiab] OR “adjusted indirect comparison”[tiab] OR (systematic*[tiab] AND review*[tiab]) OR ((mixed[tiab] OR indirect[tiab]) AND treatment*[tiab] AND comparison*[tiab]) OR (simulated[tiab] AND treatment*[tiab] AND comparison*[tiab]) OR (match*[tiab] AND adjust*[tiab] AND (indirect[tiab] OR comparison*[tiab])) OR (comparative[tiab] AND effectiveness[tiab]) OR (nma[tiab] AND (network[tiab] OR metaanalysis[tiab] OR “meta analysis”[tiab])) OR (itc[tiab] AND (indirect[tiab] OR treatment*[tiab] OR comparison*[tiab])) OR (mtc[tiab] AND (mixed[tiab] OR treatment*[tiab] OR comparison*[tiab])) OR (maic[tiab] AND (match*[tiab] OR adjust*[tiab] OR indirect[tiab] OR comparison*[tiab])) OR (stc[tiab] AND (simulated[tiab] OR treatment*[tiab] OR comparison*[tiab])))	319885
#11	Search ((#1 AND #10)) AND ("2018/01/01"[Date - Publication] : "3000"[Date - Publication])	12

No.	Query	Results
#12	Search (#9 OR #11)	533
#13	Search (rat[ti] OR rats[ti] OR rodent[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR hamster[ti] OR hamsters[ti])	1415407
#14	Search (#12 NOT #13)	527
#15	Search (pubstatusaheadofprint OR inprocess[sb])	776692
#16	Search (#14 AND #15)	19

Cochrane (CENTRAL, CDSR)

Platform: Cochrane Library

URL: https://www.cochranelibrary.com/advanced-search

Date searched: 11-Oct-2019

Hits: 115 (112 CENTRAL, 3 CDSR)

Study filters: None

Table 131: Cochrane search string (CENTRAL, CDSR)

No.	Search	Results
#1	MeSH descriptor: [Mucopolysaccharidosis IV] explode all trees	13
#2	(morquio* OR morqio* OR morkio* OR brailsford* OR keratosulfaturia* OR osteochondrodystrophia* OR GALNS* OR “N acetylgalactosamine 6 sulfatase” OR “N acetylgalactosamine 6 sulfate” OR “n acetyl d galactosamine 6 sulfate 6 sulfohydrolase” OR “n acetyl d galactosamine 6 sulphate 6 sulfohydrolase” OR “n acetylgalactosamine 6 sulphate sulfatase” OR MPSIV* OR “MPS IV” OR “MPS IVA” OR “IV MPS” OR “IVA MPS” OR MPS4* OR “MPS 4” OR “MPS 4A” OR “4 MPS” OR “4A MPS” OR ((“typ? 4” OR “typ? iv” OR typ?4 OR typ?iv OR “typ? 4a” OR “typ? iva” OR typ?4a OR typ?iva) NEAR/5 (MPS* OR muco* OR muko*)) OR (typ* NEAR/3 (four OR “4” OR “4A” OR IV OR IVA) NEAR/5 (MPS* OR muco* OR muko*)) OR (familial NEAR/3 osseous NEAR/3 dystrophy) OR (kerato NEAR/3 sulfaturia) OR ((mucopolysaccharidos* OR mucopolysacharidos* OR mukopolysaccharidos* OR “muco polysaccharidosis” OR “muco polysaccharidoses”) NEAR/7 (four OR “4” OR “4A” OR IV OR IVA OR “typeIV” OR “type4”))):ti,ab,kw	116
#3	#1 OR #2 in Cochrane Reviews, Trials	115

DARE

DARE databases (

Table 132) were searched as follows:

URL: https://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp

Search terms: Morquio OR mucopolysaccharidosis

Search date: 18-Dec-2019

Hits: 7

Relevant: 0

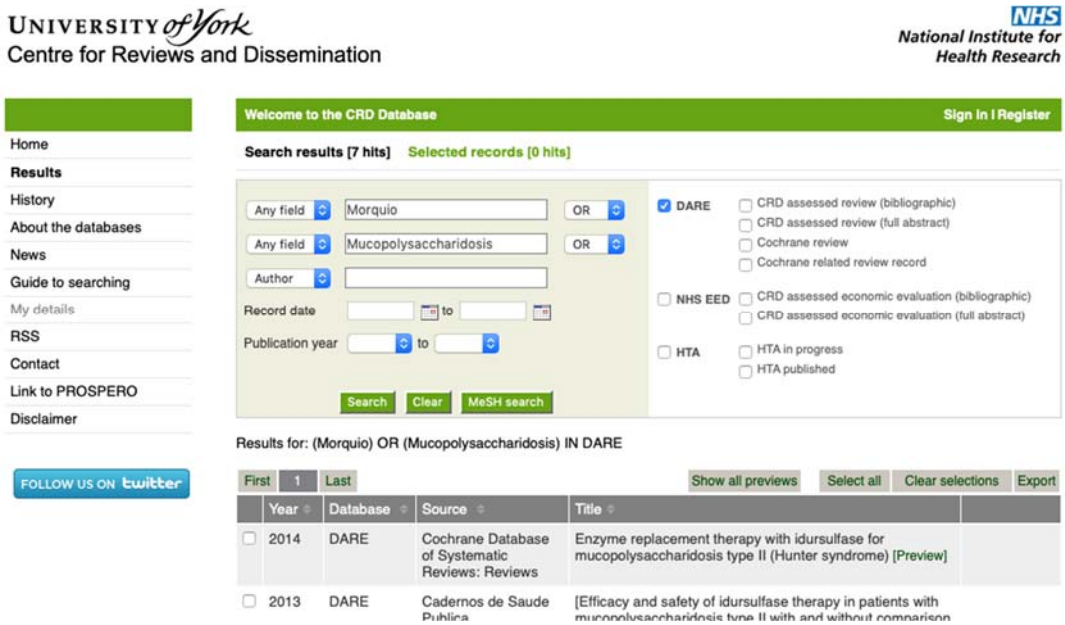

Table 132: DARE databases hand-searching

Database	Search method	Date span	Date searched
DARE	Searched for: (morquio OR mucopolysaccharidosis) in Any field	From database inception to 31st March 2015 (database closed)	18-Dec-2019

Abbreviations: DARE, Database of Abstracts of Reviews of Effects

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Conferences and journals

Conferences searched and studies included are detailed in Table 133 below. Three articles were identified as being relevant for inclusion (Adam et al., 2019a, Hughes et al., 2019a, Mukherjee et al., 2019a). Seven further abstracts were not eligible but were noted in the report (Adam et al., 2019b, Bozzo et al., 2019, Del Toro, 2018, Donis, 2017, Ficicioglu et al., 2019a, Mitchell, 2018, Mitchell et al., 2019a).

Table 133: Conference proceedings

Research meeting	Source	Search terms (hits, relevant, added)
Program and Abstracts WORLD Symposium 2019 15th Annual Research Meeting	Molecular Genetics and Metabolism 2019, Volume 126, Issue 2, Pages S1-S172	MPS IVA (5, 2, 1 Adam 2019a(Adam et al., 2019a)) Mucopolysaccharidosis (41, 0, 0) Morquio (11, 1, 0+ Adam 2019a(Adam et al., 2019a))
Program and Abstracts WORLD Symposium 2018	Molecular Genetics and Metabolism 2018, Volume 123, Issue 2, Pages S15+	MPS IVA (3, 1, 0) Mucopolysaccharidosis (44, 0, 0) Morquio (6, 1, 0*)
SSIEM 2019, Rotterdam, NLD	SSIEM 2019 abstract book	MPS IVA (21, 0, 0) Mucopolysaccharidosis (71, 0, 0) Morquio (36, 2, 2#)
SSIEM 2018, Athens, Greece	SSIEM 2018 JIMD (2018) 41 (Suppl 1):S1-S36 (titles) and JIMD (2018) 41 (Suppl 1):S37-S219 (abstracts), via Deepdyve.com	MPS IVA (6, 0, 0) Mucopolysaccharidosis (37, 0, 0) Morquio (0, 0, 0)

Abbreviations: MPS, mucopolysaccharidosis; NLD, The Netherlands; SSIEM, Society for the Study of Inborn Errors of Metabolism
+ Not added to dataset, as this abstract was already identified via MPA IVA search term
* Hendriksz abstract (Safety, efficacy, and immunogenicity of elosulfase alfa in patients with Morquio A syndrome participating in 2 sequential open-label studies (MOR-002/MOR- 100), representing 5 years of treatment) not included as child abstract to Hendriksz 2018a FP.
# Hughes 2019(Hughes et al., 2019a) and Mukherjee 2019(Mukherjee et al., 2019a) added to dataset

Cross-referencing

One citation was added to the dataset by cross-referencing from the Utilities SR (Lampe et al., 2015)

Further hand-searching

- Reference lists of included papers and of relevant recent SRs (Clark et al., 2018, Moretto et al., 2018, Nagao et al., 2018, Schrover et al., 2017, Yap and Savarirayan, 2016) identified during screening were searched, from which 4 citations were identified for inclusion (Finnigan et al., 2018, Hendriksz et al., 2014c, Jones et al., 2015, BioMarin, 2013) and 2 were noted in the report(Couprie et al., 2010, Harmatz et al., 2013).
- PubMed e-alerts tracked from 11-Oct-2019 until 13-Nov-2019 cut-off date: 0 relevant.
- Google – for full texts of abstracts identified during screening: 1 relevant and included (Pintos-Morell et al., 2018).

17.1.6 The inclusion and exclusion criteria

The inclusion and exclusion criteria used to select studies from the literature are given in Table 10 and Table 11below:

Table 134. Inclusion criteria used for clinical studies

Characteristic	Inclusion criteria
Population	MPS IVA (Morquio syndrome) Any age group (children or adults)
Mixed populations	Data reported for paediatric and adult populations (mixed data) is also eligible. Where reported separately, the mixed and separate population data will be extracted.
Interventions/ comparators	In MPS IVA, at least one treatment arm has a licensed dose of ERT e.g. ESA 2mg/kg of body weight given once per week by i.v. infusion over at least 4 hours
Outcomes	Study reports any of the following outcomes of interest: Endurance assessments (6MWT, T25FW/MSFC, stair climb test, pinch/grip test, functional dexterity test) Pain Fatigue Psychological assessments Urinary KS Heart function

Characteristic	Inclusion criteria
	Lung function Survival Audiometry tests Sleep apnoea Corneal clouding Muscle strength HRQoL, MPS HAQ and ADL (listed only)
Study design	RCTs, non-RCTs, single arm/case series SRs/NMAs*
Date limits	Unlimited
Child abstract	Sub-study abstract with unique data that could be reffered to
Publication type	Errata Original articles Technology appraisal documents, if original source not available elsewhere
Languages ¶	Electronic searching will not be limited by English language Any non-English language articles deemed relevant will be discussed with BioMarin to decide on final inclusion. For non-English language articles that are included, Vendor will utilise existing BioMarin support to translate and/or extract relevant information from included articles (if needed +)

Abbreviations: ADL, activities of daily living; ERT, enzyme replacement therapy; ESA, Elosulfase alfa; HRQoL, Health Related Quality of Life; HSCT, hematopoietic stem cell transplantation; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVA, Mucopolysaccharidosis type IVA; MSFC, multiple sclerosis functional composite; 6MWT, 6-minute walk test; NMA, Network meta-analysis; SR, Systematic Review; T25FW, timed 25-foot walk test
* Relevant SRs and meta-analyses will be kept in at 1st pass for cross-referencing/bibliography checking purposes (flagged in Endnote) but will be excluded at 2nd pass. Case reports of interest will be excluded but tagged.
+ Vendor's language capabilities include English, Czech, Danish, French, German, Hungarian, Italian, Polish,
Portuguese and Spanish.

Table 135. Exclusion criteria used for clinical studies

Characteristic	**Exclusion code & criterion**	**Explanatory notes**
Publication type	e1 pub: Publication type not of interest	e.g. editorials, commentaries, letters, notes, protocol-only articles.
Duplicate	e1 dup: Duplicate/copy	Exact duplicates or copy abstracts, for example where the content is almost identical. If there are discrepancies in the actual data reported, then both will be retained and the discrepancy noted
Child abstract	e1/e2 child: Child abstract or sub-study with no unique data	To be determined at 1st or 2nd pass stage

Languages	e2 lang: Non-English language article agreed between BioMarin and Vendor to be ineligible (+)	Non-English language articles deemed potentially relevant will be discussed with BioMarin to decide on final inclusion.
Population	e1/e2 pop: Population not of interest e.g. non-human data or mixed patient populations (e.g. MPS IVA and other MPS types without MPS IVA data reported separately) <80% of enrolled patients are of the population interest	Where non-human and human data is reported the study will be included if the human data is of relevance Papers where 80% of the population is of interest will be included, or papers where subgroup data with the population of interest are reported separately
Mixed population	e2 mix:	
Interventions / comparators	e1/e2 comp: Treatment in MPS IVA not of interest (e.g. HSCT, gene therapy, symptomatic treatment (physiotherapy / surgery) No comparator of interest or unlicensed dose for treatment of interest (e.g. every other week dosing) without a licensed treatment arm of interest	Treatments of interest in MPS IVA are ERT e.g. ESA, etc.
Sample size	e1 size	<10 patients enrolled (>=10 is includable)
Study design	e1/e2 design: Study design not of interest (e.g. case reports, n=1 before-and-after studies, PK/PD study only, (non-systematic) reviews, observational data, SRs/NMAs	SRs and meta-analyses kept in at 1st pass for cross-referencing purposes but will be excluded at 2nd pass. Case reports of interest will be excluded but tagged.
	Phase 1 only trials	Phase I/II studies reporting phase 2 data are eligible. Phase 1 only studies, or phase I/II studies reporting only the phase 1 data are excluded
	Retrospective studies	
	Case reports	Case series (n>10) may be relevant but not individual case reports
	PK/PD study only	No outcome of interest
	Cluster randomised trials	Individual subjects not randomised
	Non-systematic reviews	Any particularly interesting clinical-type reviews may be noted for discussing in the report. However, in general non-systematic reviews will be excluded.

	SRs/MAs/NMAs	Relevant SRs* and MAs are kept in at 1st pass for cross-referencing purposes but will be excluded after 2nd pass, except if MA data not available elsewhere
	Post-hoc pooled analyses	To avoid the same data being included twice. The original trials going in to the pooled analysis, if relevant, will be included.
	Pilot studies	Not robust enough evidence for use
	Economic analyses or budget impact analyses	Clinical outcomes only
	In vitro studies or animal studies	Human in vivo only
Outcomes	e1/e2 out: No outcome of interest	Outcomes not of interest, as they are of little use for clinical management, include urinary GAG tests. Growth and height decreases (due to kyphosis or knee valgus) Immunogenicity will not be collated. While HRQoL outcomes are of interest, these will be captured and extracted in the QoL SR. Those HRQoL values measured will be listed. Papers reporting only incidence or prevalence estimates of MPS IVA will be excluded but tagged.
Date limits	e1/e2 date: No restrictions on original articles. Pre-2018 SRs/meta-analyses excluded	

Abbreviations: ERT, enzyme replacement therapy; ESA, Elosulfase alfa; GAG, glycosaminoglycan; HRQoL, Health Related Quality of Life; HSCT, hematopoietic stem cell transplantation; MPS IVA, Mucopolysaccharidosis type IVA; NMA, Network meta-analysis; SR, Systematic Review;
+ Vendor's language capabilities include English, Czech, Danish, French, German, Hungarian, Italian, Polish, Portuguese and Spanish.
* SRs and meta-analyses will be kept in at 1st pass for cross-referencing/bibliography checking purposes (flagged in Endnote) but will be excluded at 2nd pass. Case reports of interest will be excluded but tagged.

17.1.7 Excluded studies

Table 136. Summary of citations excluded on basis of title and abstract (n=554)

Reason for exclusion	Number excluded	Exclusion code: e1
Population	300	e1 pop
Mixed population	0	e1 mix

Comparators	21	e1 comp
Study design	142	e1 design
Outcome	50	e1 out
Publication type	3	e1 pub
Duplicate/copy	32	e1 dup
Child publications	6	e1 child
Sample size <10	0	e1 size
Total excluded on basis of title/abstract	*554*	

Abbreviations: child, sub-study with no unique information; comp, comparator; dup, duplicate/copy; e1, excluded at title/abstract screening stage; mix, mixed; out, outcome; pop, population; pub, publication

Table 137. Excluded studies at full text review (n=51)

Author, Year	Exclusion rationale in full	Exclusion reason category
Akyol et al., 2019	Guidance/recommendations publication. Noted in Endnote. Bibliography checked. Jones 2015 and Finnigan 2018 added to dataset. Burton 2015 and Treadwell 2017 not added, as pilot studies. Hendriksz 2018 case series not added as although MPS patients, none were MPS IVA.	Study design not of interest
Auray-Blais et al., 2018	Urinary KS is reported in ERT treated and untreated pts, but no BL data were recorded and no time of ERT initiation and comparison not possible as groups had age differences. Authors indicate no conclusion can be drawn regarding impact of trt on uKS.	Study design not of interest
Auray-Blais et al., 2016	Urinary KS is reported in ERT treated and untreated pts, but no BL data were recorded and no time of ERT initiation and comparison not possible as groups had age differences. Authors indicate no conclusion can be drawn regarding impact of trt on uKS.	Study design not of interest
Baldo et al., 2015a	Study looking at GAG storage in MPS IVA patients on ESA. This outcome is not of interest for our SR.	No outcome of interest
Baldo et al., 2015b	Child abstract to Baldo 2015a	Sub-study/child citation (no additional data)
Blundell et al., 2013	Reported results of a visual attention task (search speed) for 5 MPS IVA patients	No outcome of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
Clark et al., 2018	SR of airway management in MPS. Bibliography checked. Table 2 reports difficult intubation for case-series enrolling mixed MPS patients and reporting the MPS IVA result separately but this outcome is not eligible for inclusion.	Study design not of interest
Davison et al., 2013	Case series of 14 patients examining cognitive outcomes. Although of interest it is not clear whether or not patients were under any treatment.	Comparator not of interest
El Moustafa et al., 2016	Abstract only article reporting reference ranges for men and women for diagnostic enzymes in MPS IVA patients (and other MPS types) for Turkey	No outcome of interest
Fesslová et al., 2009	Reported cardiac anomalies in 10 Morquio patients, but it was not reported which patients were or were not on ERT	Comparator not of interest
Giugliani et al., 2015	Sub-study AB to Hendriksz 2016b and Hendriksz 2016c FPs	Sub-study/child citation (no additional data)
Graham et al., 2014	AB only article introducing MARS but with no results reported	No outcome of interest
Guffon et al., 2016	MARS BL data (median age of 59 ESA-treated pts and 13 untreated pts) but no results. AB only article.	No outcome of interest
Harmatz et al, 2015a	Sub-study AB (providing 6MWT result) to Hendriksz 2016b and Hendriksz 2016c FPs. The abstract was available on deepdyve in SSIEM conference proceedings book.	Sub-study/child citation (no additional data)
Harmatz et al., 2015b	Observational data from the MorCAP study of untreated MPS IVA patients	Study design not of interest
Hendriksz et al., 2013a	Sub-study AB to Hendriksz 2014 FP, no additional data	Sub-study/child citation (no additional data)
Hendriksz et al., 2012	Sub-study AB to Hendriksz 2018a. Results also on registry record (EUCTR, 2009)	Sub-study/child citation (no additional data)
Hendriksz et al., 2015c	International guidelines document. Bibliography checked. Noted in report.	Study design not of interest
Hendriksz et al., 2016a	Review article of HRQoL in MPS. Bibliography checked. Harmatz 2013 relevant	Study design not of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
	(reporting MPS HAQ) but this is already included in the Utilities SR so not added here. Hendriksz 2014c added to dataset / cross-referenced to utilities SR. Hendriksz 2014a not added as already included in Utilities SR. Ali 2015 not added (SF-36) as this abstract-only article reported no actual data. Brands 2015 not added as although it reports SF-36 it does so for a mixed MPS population. The referenced Lavery 2015 poster could not be identified: however, Lavery 2017 was included already in the utilities SR with the EQ-5D data. Harmatz 2015 (AB) not added (pain outcomes) as was a pilot study. Hendriksz 2015d and Hendriksz 2014 not added as already included in Clin SR. Lamps 2015 and Harmatz 2013b not added as already included in Utilities SR.	
Hendriksz et al., 2017	Sub-study AB to Hendriksz 2018b reporting MPS HAQ. No additional data in AB.	Sub-study/child citation (no addtional data)
Kampmann et al., 2016	Observational data for cardiac function in MPS IVA patients.	Study design not of interest
Kampmann et al., 2014	Child abstract to Kampmann 2016 FP.	Sub-study/child citation (no addtional data)
Keilmann et al., 2016	Reports mucosal alterations of the larynx and hypopharynx for mixed MPS population including 13 MPS IV patients (not specified if A or B). Results are reported by MPS type in figures but these outcomes are not eligible for this SR.	No outcome of interest
Kenth et al., 2019	Retrospective longitudinal analysis of pulmonary function with and without ERT (UK)	Study design not of interest
Leong et al., 2019	Natural history cohort of MPS IVA patients in Malaysia / no treatments reported.	Comparator not of interest
Lin, et al. 2014a	Examines hearing loss reporting baseline results (prior to ERT) for 9 MPS IVA patients.	Comparator not of interest
Lin et al., 2014b	Reports lung function in mixed MPS population, 16/35 of whom were MPS IVA. However the results are not reported	Population not of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
	separately for the MPS IVA subgroup.	
Long et al., 2017	Immunogenicity not an eligible outcome. Reports also 6MWT, 3MSCT and uKS by TAb titer: noted in report but not extracted.	No outcome of interest
Matsubara et al., 2017	Interesting initial assessment of ERT effect on CNS in MPS patients. However, of the 17 enrolled MPS patients, none was MPS IVA.	Population not of interest
Montaño et al., 2007	International Morquio A registry data from before ESA available, and no treatments (diet status) indicated	Comparator not of interest
Moretto et al., 2018	Systematic review of evidence to provide guidance for anaesthesia in MPS patients. MPS IVA data are discussed separately, but the outcome is not eligible for inclusion in this SR.	Study design not of interest
NCT, 2012	Pilot study (MOR-008) that was terminated early (NCT01609062)	Study design not of interest
Nelson et al., 1988a	Discusses diagnostic methods using 12 case reports	Study design not of interest
Nelson et al., 1988b	Reports dental changes in MPS IVA using 9 case reports	No outcome of interest
Nelson et al., 1988c	Reports odontoid dysplasia in 12 case reports	No outcome of interest
Pintos-Morell et al, 2015	AB article reporting real world experience in 7 pts in ESP. FP article identified via Google (Pintos-Morell 2018), so this AB superseded.	Sub-study/child citation (no additional data)
Politei et al., 2015	Non-systematic review article in Spanish. Bibliography checked: Couprie 2010 added (although a retrospective study, provides corneal clouding data on 20 Morquio patients). Tunkel 2012, Davison 2013 already included.	Study design not of interest
Regier et al., 2016	Non-systematic review on the role of ESA in MPS IVA. Bibliography checked - Briefing document for Advisory Committee added to dataset. Hendriksz 2014/2015 already included. Jones 2015 already added as a hand-search.	Study design not of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
Rekka et al., 2012	Reports oral findings in 3 cases of MPS IVA in India	No outcome of interest
Santra et al., 2014	Sub-study AB to Hendriksz 2018a. This AB superseded and provides only the interim results.	Sub-study/child citation (no additional data)
Schrover et al., 2017	Systematic review to estimate the MCID for 6MWT. Bibilography checked (no data added as Hendriksz 2014 and 2016 already included). Noted in report as compares the MCID obtained to the 6MWT results with ESA in MPSIVA.	Study design not of interest
Schweighardt et al., 2015	Reports immunogenicity and potential HAE associations by immunogenicity status for MOR-004	No outcome of interest
Sornalingam et al., 2019	Observational study with only 4 MPSIV patients included. Only 1 of these pts is specified as being MPSIVA.	Study design not of interest
Theroux et al., 2018	Reports tracheal abnormalities in cohort of 60 MPS IVA patients, but not lung function	No outcome of interest
Tomatsu et al., 2016	Reports on tracheal narrowing/obstruction in a series of cases	No outcome of interest
Tomatsu et al., 2017	Reports on tracheal narrowing/obstruction in a series of cases	No outcome of interest
Tunkel et al., 2012	Describes hearing loss in skeletal dysplasias, reporting results separately for 3 Morquio cases. However, it is not stated whether these patients are Morquio A or B, so population is not confirmed.	Population not of interest
Tuysuz et al, 2019	Description of 26 Morquio pts from TUR, but no treatments or diet statu are indicated. AB only article from the 50th ESHG Conference.	Comparator not of interest
Wasielica-Poslednik et al, 2014	Reports corneal clouding in 8 MPS IV pts, but not specified if MPS IVA or IVB	Population not of interest
Yap et al., 2016	Non-systematic review. Bibliography checked - no data added to dataset as Hendriksz 2014 and 2015 already included in our dataset.	Study design not of interest
Yasuda et al., 2016	Reports ADL scores for MPS IVA patients. Not an eligible	No outcome of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
	outcome for inclusion, but noted for listing in the report	

Abbreviations: 6MWT, 6-minute walk test; AB, abstract; ADL, Activities of Daily Living; BL, baseline; ERT, Enzyme Replacement Therapy; ESA, elosulfase alfa; ESHG, European Society of Human Genetics; EU-CTR, European Union Clinical Trials Register; FP, full paper; GAG, glycosaminoglycan; HAE, hypersensitivity adverse event; HAQ, Health Assessment Questionnaire; HRQoL, health-related quality-of-life; MARS, Morquio A Registry Study; MCID, minimum clinically important difference; MPS, Mucopolysaccharidosis; pts, patients; SF-36, short-form 36; SR, Systematic Review; SSIEM, Society for the Study of Inborn Errors of Metabolism; TUR, Turkey; UK, United Kingdom

Of the studies excluded during electronic screening or hand-searching (not meeting the eligibility criteria), those worthy of note (n=32) were:

- Adam et al. 2019b described changes reported by MPS IVA patients during the collection of Patient Reported Outcome (PRO) data as part of the MAA in England. These changes included changes in energy levels, walking/movements, sleep/tiredness, thinking/learning and general health, in treatment-naïve and in clinical trial patients. Macaulay et al. 2016 described MAAs in general terms as a new model for reimbursement in England of non-oncology drugs, and Roberts et al. 2017 described multi-stakeholder engagement as a means to treatment access in MPS IVA and as a model for ultra-rare diseases.
- Bozzo et al. 2019 reported improved respiratory function and walking ability with ESA in 4 Brazilian MPS IVA patients and that no AEs were reported. Of the 4 patients, prior to treatment, 1 patient was ambulatory and 3 were non-ambulatory. After treatment, 1 of the non-ambulatory patients started to walk again without support.
- Cho et al. 2014 describe MPS patients in South Korea and the Asia-Pacific MPS Registry.
- Couprie et al. 2010 report ocular manifestations in MPS IVA in a retrospective study at a hospital in France and Wasielica-Poslednik et al. 2014 measurements with an ocular response analyser compared to those with gold standard techniques in MPS IV (n=8) and MPS VI (n=9) patients (AB only article).
- Del Toro et al. 2018 reported two-year follow-up of elosulfase alfa in paediatric MPS IVA patients. This AB was identified via conference searching but the AB itself was not obtainable, so eligibility could not be confirmed.

- Doherty et al. 2019 reported growth outcomes of MPS IVA patients on ERT, as did Montano et al. 2008.
- Donis, 2017 reported how early treatment with elosulfase alfa was associated with better outcomes in MPS IVA patients, as did Ficicioglu et al. 2019.
- Harmatz et al. 2013 reported MorCAP baseline data and longitudinal data were reported in Harmatz et al. 2015b. Further natural history data, but from one family, were reported by Matalon et al. 2018 (although the AB for this could not be obtained). The international MARS registry was reported in Montano et al. 2007.
- Recommendations for the management of MPS IVA patients were reported by Harmatz et al. 2018 and international guidelines by Hendriksz et al. 2015c. Continued challenges were highlighted in Puckett et al. 2017.
- Observational data for cardiac function in MPS IVA pts were reported in Kampmann et al. 2016.
- Lavery and Hendriksz 2017 reported mortality in MPS IVA patients in 1975-2010 in the UK.
- Immunogenicity data for MOR-005 were reported in Long et al. 2017.
- Mitchell et al. 2018 & 2019 reported on elosulfase alfa responses in a large population of MPS IVA patients in Quebec, from a retrospective case series (the 2018 AB could not be obtained, but the 2019 AB was available).
- Pimentel et al. 2017 reported improved QoL with elosulfase alfa in 1 patient who was in a wheelchair.
- The *in vitro* and *in vivo* characterisation of n-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme produced in pichia pastoris (rather than in Chinese Hamster Ovary (CHO) cells) was described by Rodriguez-López et al. 2017.
- The MCID for the 6MWT in a number of (non-MPS IVA) diseases was reviewed by Schrover et al. 2017. The mean MCID for 6MWT was a 7% change (range 3-15%) using anchor-based methods and a 9% change (range 4-16%) using distribution-based methods. The mean change in the ESA RCT and its extension study after placebo (PLA) adjustment was 14.9% improvement from BL to wk 24 and, in an MPP population at 2 yrs, by 20.9%. Over this time period (2 yrs)

in the MorCAP population, untreated pts had a 6.9% reduction in 6MWT.

- Theroux et al. 2018 found that severe tracheal abnormalities complicating anaesthesia were common and further detail on severe tracheal obstruction and novel surgical reconstruction for this have been reported.
- ADL in MPS IVA patients, untreated or on ERT and in healthy controls, was described in a FP by Yasuda et al. 2016 and its linked AB, Tomatsu et al. 2017.

A further ten studies were noted as reporting epidemiological prevalence/incidence data in MPS IVA (Leong et al., 2019; Yap et al., 2016; Da Costa Ferriera Neri et al., 2017; Gómez, 2012; Hunag et al., 2012; Leadley et al., 2014; Lin et al., 2009; Pachajao et al., 2017; Tomatsu et al., 2017b; Vu et al., 2017).

17.1.8 The data abstraction strategy

Results from the database searches were downloaded via Endnote (for removing duplicates) and into an online tool for screening, Rayyan: http://rayyan.qcri.org, (an internet-based reference management system for SR screening, developed by the Qatar Computing Research Institute) . This was used to manage citation screening during first pass (abstract and title review stage).

Abstracts were screened by one senior reviewer. As per good practice, we produced a table counting citations excluded at abstract stage (e1) by exclusion category. In the instance of borderline eligibility cases, the precautionary principle was applied, and these were accepted into second pass.

Papers retained for second pass (full paper review stage) were exported to an Excel file for further review. Second pass papers were tagged in Endnote (i2s).

Full texts were first sought within Endnote (full text automated search). Full texts not available via Endnote or open access online were viewed via DeepDyve.com. Those unavailable via DeepDyve were requested via the manufacturer.

Full papers were reviewed by two reviewers independently in a blinded fashion. Discrepancies were discussed and resolved. If a paper remained borderline a third appropriate reviewer adjudicated. As per good practice we produced a table of citations excluded at full text stage (e2) with full rationale for exclusion.

17.2 Appendix 2: Search strategy for adverse events

The following information should be provided.

17.2.1 The specific databases searched, and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search (item **Error! Reference source not found.**) were extracted and reported in t he section 9.7.2.

17.2.2 The date on which the search was conducted.

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search (item **Error! Reference source not found.**) were extracted and reported in t he section 9.7.2.

17.2.3 The date span of the search.

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search (item **Error! Reference source not found.**) were extracted and reported in t he section 9.7.2.

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search (item **Error! Reference source not found.**) were extracted and reported in t he section 9.7.2.

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search (item **Error! Reference source not found.**) were extracted and reported in t he section 9.7.2.

17.2.6 The inclusion and exclusion criteria.

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search (item **Error! Reference source not found.**) were extracted and reported in t he section 9.7.2.

17.2.7 The data abstraction strategy.

No specific literature review was undertaken to identify studies on adverse events. All safety data reported in the studies identified in the clinical search (item **Error! Reference source not found.**) were extracted and reported in t he section 9.7.2.

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The following electronic databases were searched.

- Embase via the Embase.com platform
- Medline via the Embase.com platform
- Medline InProcess and electronic publications ahead-of-print via PubMed
- The Cochrane Library's NHS EED and HTAD databases via the Centre for Reviews and Dissemination, University of York (CRD) website (https://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp).

17.3.2 The date on which the search was conducted.

The dates on which the searches were conducted:

18 October 2019 (Embase.com)

18 October 2019 (Pubmed)

18 December 2019 (NHS EED, HTAD and all hand-searching)

4 November 2020:

- An updated HRQoL search was done in November 2020. The search terms and inclusion/ exclusion criteria were same as the original search of November 2019. The new search generated 20 articles at the 1st

pass (EMBASE/ MEDLINE), and 8 articles after the 2nd pass. The summary of these 8 new articles is summarized in section **Error! R eference source not found.** below.

- An updated economic search was done in November 2020. The search terms and inclusion/ exclusion criteria were also same as the original search of November 2019. The new search generated 19 articles at the 1st pass (EMBASE/ MEDLINE), and 5 articles after the 2nd pass. The summary of these 5 economic articles are presented in section **Error! R eference source not found.** below;

17.3.3 The date span of the search.

The date span of the search for economic data[16]:

Embase – Database inception (1974) to date of search

MEDLINE – Database inception (1966) to date of search

Pubmed – Database inception to the day prior to search

NHS EED – Database inception to 31st March 2015 (database closed)

HTAD – Database inception to 31st March 2018 (new records no longer being added by CRD)

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strings employed are given below for Embase and MEDLINE (Table 129), MEDLINE in-process and e-publications ahead-of-print (Table 130).

Embase/medline search string

[16] Cost and resource use data were limited from 2010 onwards (see Appendix 4)

Platform: Embase.com

URL: https://www.elsevier.com/solutions/embase-biomedical-research

Date searched: 18-Oct-2019

Hits: 87

Economic filter: adapted from EMBASE G filter of Glanville et al. 2009(Glanville et al., 2009a)

Table 138: Embase and Medline search string

No.	Query	Results
#1	'morquio syndrome'/exp OR morquio*:de,ab,ti OR morqio*:de,ab,ti OR morkio*:de,ab,ti OR brailsford*:de,ab,ti OR keratosulfaturia*:de,ab,ti OR osteochondrodystrophia*:de,ab,ti OR galns*:de,ab,ti OR 'n acetylgalactosamine 6 sulfatase':de,ab,ti OR 'n acetylgalactosamine 6 sulfate':de,ab,ti OR 'n acetyl d galactosamine 6 sulfate 6 sulfohydrolase':de,ab,ti OR 'n acetyl d galactosamine 6 sulphate 6 sulfohydrolase':de,ab,ti OR 'n acetylgalactosamine 6 sulphate sulfatase':de,ab,ti OR mpsiv*:de,ab,ti OR 'mps iv':de,ab,ti OR 'mps iva':de,ab,ti OR 'iv mps':de,ab,ti OR 'iva mps':de,ab,ti OR mps4*:de,ab,ti OR 'mps 4':de,ab,ti OR 'mps 4a':de,ab,ti OR '4 mps':de,ab,ti OR '4a mps':de,ab,ti OR ((('typ? 4' OR 'typ? iv' OR typ?4 OR typ?iv OR 'typ? 4a' OR 'typ? iva' OR typ?4a OR typ?iva) NEAR/5 (mps* OR muco* OR muko*)):de,ab,ti) OR ((typ* NEAR/3 (four OR '4' OR '4a' OR iv OR iva) NEAR/5 (mps* OR muco* OR muko*)):de,ab,ti) OR ((familial NEAR/3 osseous NEAR/3 dystrophy):de,ab,ti) OR ((kerato NEAR/3 sulfaturia):de,ab,ti) OR (((mucopolysaccharidos* OR mucopolysacharidos* OR mukopolysaccharidos *OR 'muco polysaccharidosis' OR 'muco polysaccharidoses') NEAR/7 (four OR '4' OR '4a' OR iv OR iva OR 'typeiv' OR 'type4')):de,ab,ti)	**3072**
#2	((cost NEAR/3 effectiveness):ab,ti) OR costeffectiveness:ab,ti OR 'cost utility':ab,ti OR costutility:ab,ti OR ((life NEAR/3 (year OR years)):ab) OR qaly:ab OR (cost:ab AND costs:ab) OR 'cost effective':ti OR ((cost:ab OR costs:ab) AND 'controlled study'/exp)	**326624**
#3	'economic evaluation'/exp OR ((cea NEAR/3 (cost* OR effectiveness OR analys*)):de,ab,ti) OR ((cua NEAR/3 (cost OR utility OR analys*)):de,ab,ti)	**295062**
#4	#2 OR #3	**500567**
#5	#1 AND #4	**51**
#6	'cost of illness'/exp OR 'health care cost'/exp OR 'drug utilization'/exp OR 'productivity'/exp OR 'health care utilization'/exp OR cost$:ab,ti OR resource$:ab,ti OR expense$:ab,ti OR employment:ab,ti OR productivity:ab,ti OR ((expenditure NEAR/2 energy):ab,ti) OR (((drug* OR healthcare OR 'health care' OR 'health service' OR 'health services') NEAR/3 (use OR utilisation OR utilization)):ab,ti) OR ((coi NEAR/3 illness*):ab,ti) OR 'willingness to pay':ab,ti OR willingnesstopay:ab,ti OR 'willingnessto pay':ab,ti OR 'willingness topay':ab,ti OR rswtp:ab,ti OR wtp:ab,ti	**1530265**
#7	'budget'/exp OR ((budget NEAR/3 impact NEAR/3 (analys* OR assess*)):ab,ti) OR ((bia NEAR/3 (budget OR impact OR analys* OR assess*)):ab,ti)	**31103**
#8	#6 OR #7	**1547833**
#9	#1 AND #8 AND [2010-2019]/py	**64**
#10	#5 OR #9	**95**
#11	rat:ti OR rats:ti OR rodent$:ti OR mouse:ti OR mice:ti OR murine:ti OR hamster$:ti	**1704910**

No.	Query	Results
#12	#10 NOT #11	**93**
#13	#12 AND ('chapter'/it OR 'conference paper'/it OR 'note'/it OR 'short survey'/it)	**6**
#14	#12 NOT #13	**87**

Medline in-process and e-publications ahead of print search string

Platform: Pubmed

URL: https://www.ncbi.nlm.nih.gov/pubmed

Date searched: 18-Oct-2019

Hits: 7

Economic filter: adapted from EMBASE G filter of Glanville et al. 2009(Glanville et al., 2009b)

Table 139: Medline in-process and e-publications search string

No.	Query	Results
#1	Search ("Mucopolysaccharidosis IV"[mh] OR morquio*[tiab] OR morqio*[tiab] OR morkio*[tiab] OR brailsford*[tiab] OR keratosulfaturia*[tiab] OR osteochondrodystrophia*[tiab] OR GALNS*[tiab] OR “N acetylgalactosamine 6 sulfatase”[tiab] OR “N acetylgalactosamine 6 sulfate”[tiab] OR “n acetyl d galactosamine 6 sulfate 6 sulfohydrolase”[tiab] OR “n acetyl d galactosamine 6 sulphate 6 sulfohydrolase”[tiab] OR “n acetylgalactosamine 6 sulphate sulfatase”[tiab] OR MPSIV*[tiab] OR “MPS IV”[tiab] OR “MPS IVA”[tiab] OR “IV MPS”[tiab] OR “IVA MPS”[tiab] OR MPS4*[tiab] OR “MPS 4”[tiab] OR “MPS 4A”[tiab] OR “4 MPS”[tiab] OR “4A MPS”[tiab] OR ((“typ? 4”[tiab] OR “typ? iv”[tiab] OR typ?4[tiab] OR typ?iv[tiab] OR “typ? 4a”[tiab] OR “typ? iva”[tiab] OR typ?4a[tiab] OR typ?iva[tiab]) AND (MPS*[tiab] OR mucopoly*[tiab] OR muko*[tiab])) OR (type*[tiab] AND (four[tiab] OR “4”[tiab] OR “4A”[tiab] OR IV[tiab] OR IVA[tiab]) AND (MPS*[tiab] OR mucopoly*[tiab] OR muko*[tiab])) OR (familial[tiab] AND osseous[tiab] AND dystrophy[tiab]) OR (kerato[tiab] NEAR/3 sulfaturia[tiab]) OR ((mucopolysaccharidos*[tiab] OR mucopolysacharidos*[tiab] OR mukopolysaccharidos*[tiab] OR “muco polysaccharidosis”[tiab] OR “muco polysaccharidoses”[tiab]) AND (four[tiab] OR “4”[tiab] OR “4A”[tiab] OR IV[tiab] OR IVA[tiab] OR “typeIV”[tiab] OR “type4”[tiab])))	3197
#2	Search ((cost[tiab] AND effectiveness[tiab]) OR costeffectiveness[tiab] OR “cost utility”[tiab] OR costutility[tiab] OR (life[tiab] AND (year[tiab] OR years[tiab])) OR qaly[tiab] OR (cost[tiab] AND costs[tiab]) OR “cost effective”[tiab] OR ((cost[tiab] OR costs[tiab]) AND “clinical study”[pt]))	469719
#3	Search (“Costs and Cost Analysis”[mh] OR (CEA[tiab] AND (cost[tiab] OR effectiveness[tiab] OR analys*[tiab])) OR (CUA[tiab] AND (cost[tiab] OR utility[tiab] OR analys*[tiab])))	235813
#4	Search (#2 OR #3)	623349
#5	Search (#1 AND #4)	109
#6	Search (“Cost of Illness”[mh] OR "Health Care Costs"[mh] OR "Drug Utilization"[mh] OR "Drug Utilization Review"[mh] OR "Efficiency"[mh] OR "Efficiency, Organizational"[mh] OR “Patient Acceptance of Health Care”[mh] OR cost[tiab] OR costs[tiab] OR resource[tiab] OR resources[tiab] OR expense[tiab] OR expenses[tiab] OR employment[tiab] OR productivity[tiab] OR (expenditure[tiab] AND energy[tiab]) OR ((drug*[tiab] OR healthcare[tiab] OR “health care”[tiab] OR “health service”[tiab] OR “health services”[tiab]) AND (use[tiab] OR utilisation[tiab] OR utilization[tiab])) OR (COI[tiab] AND illness*[tiab]) OR “willingness to pay”[tiab] OR willingnesstopay[tiab] OR “willingnessto pay”[tiab] OR “willingness topay”[tiab] OR RSWTP[tiab] OR WTP[tiab])	1148476
#7	Search (“budgets”[mh] OR “economics”[mh] OR (budget[tiab] AND impact[tiab] AND (analys*[tiab] OR assess*[tiab])) OR (BIA[tiab] AND (budget[tiab] OR impact[tiab] OR analys*[tiab] OR assess*[tiab])))	589510

No.	Query	Results
#8	Search (#6 OR #7)	**1509145**
#9	Search (#1 AND #8)	**69**
#10	Search (#5 OR #9)	**150**
#11	Search (rat[ti] OR rats[ti] OR rodent[ti] OR rodents[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR hamster[ti] OR hamsters[ti])	**1424665**
#12	Search (#10 NOT #11)	**146**
#13	Search (pubstatusaheadofprint OR inprocess[sb])	**776703**
#14	Search (#12 AND #13)	**7**

NHS EED and HTAD

NHS EED and HTAD databases (

Table 132) were searched as follows:

URL: https://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp

Search terms: morquio or mucopolysaccharidosis

Search date: 18-Dec-2019

Hits: 22 (4 since 2015)

Relevant: 3 but since Hayes Inc. report not available, 2 were included.(Cooper et al., 2015, IQWIG, 2017)

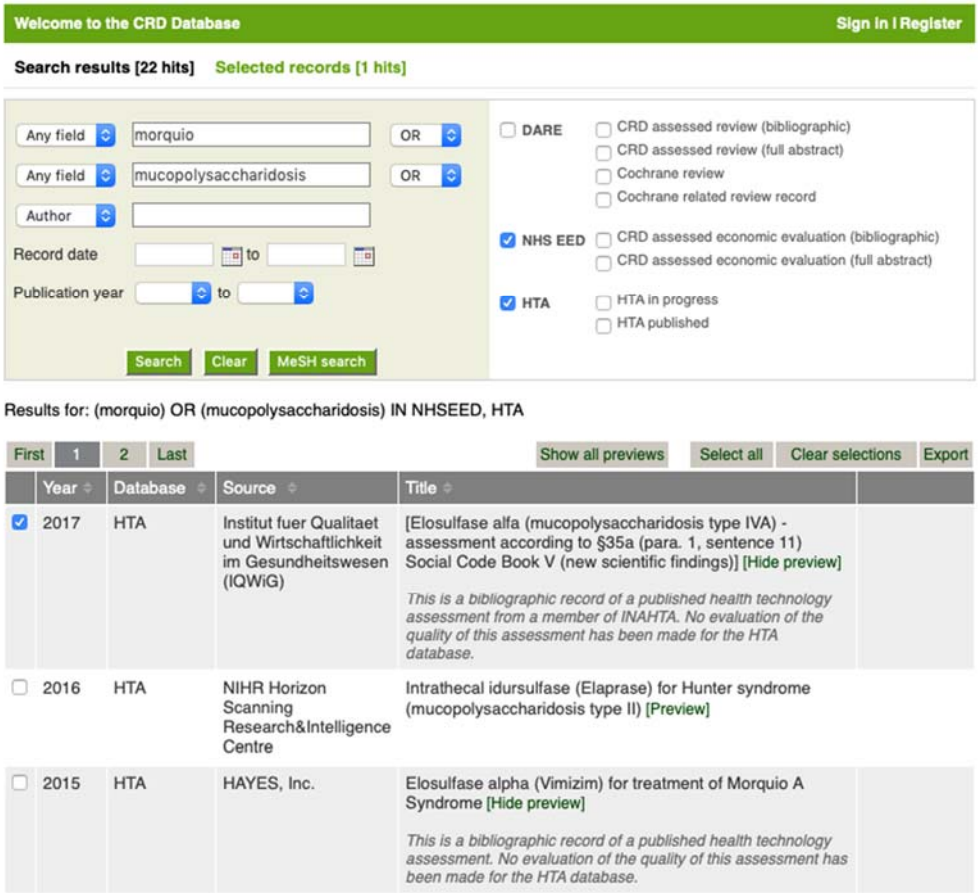

Table 140: NHS EED and HTA databases hand-searching

Database	Search method	Date span	Date searched
NHS EED	Searched for: (morquio or mucopolysaccharidosis) in Any field	From database inception to 31st March 2015 (database closed)	18-Dec-2019
HTAD	Searched for: (morquio or mucopolysaccharidosis) in Any field	From database inception to 31-Mar-2018 (new records no longer being added by CRD)	18-Dec-2019

Abbreviations: CRD, Centre for Reviews and Dissemination, University of York; HTAD, Health Technology Assessment Database; NHS EED, National Health Service Economic Evaluation Database

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Conferences and journals

Economic evaluations and costs/HCRU studies

Conferences searched are detailed in Table 133 below. 0 articles was identified as being relevant.

Table 141: Conference proceedings

Research meeting	Source	Search terms (hits, relevant, added)+
ISPOR International **18-22 May, 2019, New Orleans, LA, USA**	http://www.ispor.org/heor-resources/presentations-database/search	Morquio (0) Mucopolysaccharidosis (1, 0) MPS (0)
ISPOR International **19-23 May 2018, Baltimore, MD, USA**		Morquio (1, 0) Mucopolysaccharidosis (2, 0) MPS (1, 0)
ISPOR Europe **Nov 2019, Copenhagen, Denmark**		Morquio (0) Mucopolysaccharidosis (4, 0) MPS (2, 0)
ISPOR Europe **10-14 Nov 2018, Barcelona, SPAIN**		Morquio (0) Mucopolysaccharidosis (3, 0) MPS (1, 0)

Abbreviations: ISPOR, International Society for Pharmacoeconomics and Outcomes Research; LA, Los Angelis; MPS, mucopolysaccharidosis; USA, United States of America
+ For all ISPOR searches the Disease/disorder, Topic and Subtopic fields were set to 'All'

HTA sites

The following HTA agencies were reviewed for relevant data, using the separate search terms, morquio or mucopolysaccharidosis (NICE, CADTH, SMC) or elosulfase (AWMSG, HAS):

- National Institute for Health and Care Excellence (NICE) (England)
- Canadian Agency for Drugs and Technologies in Health (CADTH) (Canada)
- Scottish Medicines Consortium (SMC) (Scotland)
- All Wales Medicines Strategy Group (AWMSG) (Wales)
- Haute Autorité de Santé (HAS) (France)

The Canadian and International HTA database via CRD was not searched (planned at protocol stage), as the site was no longer accessible http://www.crd.york.ac.uk/PanHTA/.

There were 6 additional citations added to the dataset(AWMSG, 2016, CADTH, 2016a, CADTH, 2016b, NICE, 2015a, NICE, 2015c, SMC, 2015).

CEA registry

The Cost-Effectiveness Analysis registry was searched, searching the Methods, Ratios and Utility Weights sections, each with the separate terms morquio or mucopolysaccharidosis.

0 additional citations were added to the dataset.

Date: 18-Dec-2019

URL: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx

Search terms: morquio, mucopolysaccharidosis

Hits: 0

Relevant: 0

EconPapers

Date: 18-Dec-2019

URL: https://econpapers.repec.org/scripts/search.pf

Search terms: (mucopolysaccharidosis) in Working papers or articles in the free text field

Hits: 2

Relevant: 0

Note: Pentek et al. 2016(Pentek et al., 2016) was not relevant as the full text did not report MPS IVA data separately (there were also no UK patients). Most pts had MPS III (43%) or MPS II (27%). Angelis et al. 2015 (Pentek et al., 2016) was an SR of COI analyses. Likewise, MPS IVA data were not reported.

Further hand-searching

- Reference lists of included papers and of relevant recent SRs or CUAs identified during screening, from which 1 citation was identified, a NICE final evaluation determination(NICE, 2015b).
- PubMed e-alerts, tracked from 18-Oct-2019 until 13-Nov-2019 cut-off date: 0 relevant.

17.3.6 Excluded studies on utilities (HRQoL)

Table 142. Summary of citations excluded on basis of title and abstract (n=211)

Reason for exclusion	Number excluded	Exclusion code: e1
Population	79	e1 pop
Mixed population	8	e1 mix
Study design	15	e1 design
Outcome	85	e1 out
Publication type	0	e1 pub
Duplicate/copy	16	e1 dup
Child publications	8	e1 child
Country	0	e1 country
Total excluded on basis of title/abstract	*211*	

Abbreviations: child, sub-study with no unique information; comp, comparator; dup, duplicate/copy; e1, excluded at title/abstract screening stage; mix, mixed; out, outcome; pop, population; pub, publication

Table 143: Excluded studies at full text review (n=21)

Author, Year	Exclusion rationale in full	Exclusion reason category
Actrn et al., 2018	Registry record. SF-36 indicated to be an outcome for patients with MS, but not for their caregivers	No outcome of interest
Amatya et al., 2015	This was an SR. The seven studies that were included reporting QoL, did not report QoL for carers of MS patients.	No outcome of interest
Argyriou et al., 2011a	Reports EQ-5D-VAS and component scores of EQ-5D for carers of MS patients in Greece, but doesn't report EQ-5D index scores.	No outcome of interest
Argyriou et al., 2011b	Reports EQ-5D-VAS and component scores of EQ-5D for carers of MS patients in Greece, but doesn't report EQ-5D index scores.	No outcome of interest
Buhse et al., 2008	Review (non-systematic) of caregiver burden (MS patients)	Study design not of interest
Campbell et al., 2014	Reports HRQoL for MS patients but not for their caregivers	No outcome of interest
Cohen et al., 2010	Although this paper discusses caregiver burden in relation to walking ability of the MS patient, the measure is caregiver time.	No outcome of interest
Coleman et al., 2013	Reports EQ-5D for patients in relation to patient immobility measures, but not for caregivers	No outcome of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
Euctr GB, 2009	Registry record for MOR-002, which has MPS HAQ as an outcome. The results posted however do not report the MPS HAQ results on the registry page (https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-007365-23/results#baselineCharacteristicsSection)	No outcome of interest
Euctr GB, 2010	Registry record for MOR-100, which has MPS HAQ and EQ-5D-5L as outcomes. The results posted however on the registry record do not report these outcomes (https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-021048-16/results#baselineCharacteristicsSection)	No outcome of interest
Euctr IT, 2011b	Registry record for MOR-100, which has MPS HAQ as an outcome. The results posted however on the registry record do not report this outcome (https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020199-45/results)	No outcome of interest
Gras et al., 2016	CUA in MS. Although carer costs were used in a scenario analysis, carer utilities were not reported/used.	No outcome of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
Hendriksz et al., 2016	Review of MPS HRQoL studies. Bibliography checked. No further data to add to dataset.	Study design not of interest
Hendriksz et al., 2017	Abstract sub-study to Hendriksz 2018b FP	Sub-study/child citation (no addtional data)
Jongen et al., 2016	CSI used to measure MS caregivers' strain	No outcome of interest
Khan et al., 2006	Reports CSI for carers of MS patients, but no relevant outcome for carers	No outcome of interest
Page et al., 2017	SR of disease-specific QoL for family carers of patients with neurodegenerative diseases. None of the measures are relevant, however.	Study design not of interest
Pintos-Morell et al., 2018	Only reports EQ-5D-VAS, not EQ-5D index scores, in 7 ESA patients with MPS IVA	No outcome of interest
Schrover et al., 2017	No relevant outcome. Refers to HRQoL reported in Lampe 2015 (already included in our SR)	No outcome of interest
Treadwell et al., 2017	Reports pain descriptors but no utility data	No outcome of interest
Uccelli et al., 2014	Non-comprehensive systematic review from 2013, of impact on carers of MS patients. Bibliography checked.	Study design not of interest

Abbreviations: AB, abstract; CSI, caregiver strain index; CUA, cost-utility analysis; EQ-5D, EuroQol-5 dimensions; FP, full paper; HAQ, health assessment questionnaire; HRQoL, health-related quality of life; MPS, mucopolysaccharidosis; MS, multiple sclerosis; N/A, non-applicable; NICE, National Institute of Health and Care Excellence; QoL, quality of life; SF-36, short-form 36; SR, systematic review; VAS, visual analogue scale

Of the studies excluded during electronic screening or hand-searching (not meeting the eligibility criteria), those worthy of note were:

- Argyriou et al. 2011 reported EQ-5D VAS, but not EQ-5D index values, in MS caregivers.
- Aronson et al. 1997 reported **population based** QoL[17] data for caregivers of MS patients in Canada (CAN), relating overall satisfaction with QoL in patients and in caregivers to employment status, financial income, interference with social interactions and attitude towards MS (denial, come to terms, acceptance).
- Two papers reported SF-8 for MS caregivers (Buchanan et al., 2010; Buchanan et al., 2011) and one paper (Giordano et al., 2016) reported significantly lower HRQoL on all SF-36 scales (but without reporting the values) in MS caregivers compared with Italian norms.
- Carton et al. 2000 reported the additional caregiving time required in MS as severity of MS increases, in Flanders, Belgium.
- Henkel et al. 2010 indicated in an AB only article that MPS HAQ would be collected in the Morquio Clinical Assessment Program (MorCAP). The full text publication that superseded this AB was included in our SR, Harmatz et al. 2013b.

17.3.7 Excluded studies on HCRU

Table 144. Summary of citations excluded on basis of title and abstract (n=69)

Reason for exclusion	Number excluded	Exclusion code: e1
Population	23	e1 pop
Study design	19	e1 design
Comparator	0	e1 comp
Outcome	24	e1 out
Publication type	0	e1 pub
Duplicate	1	e1 dup
Child publications	0	e1 child
Country	2	e1 country
Total excluded on basis of title/abstract	***69***	

Abbreviations: child, sub-study with no unique information; comp, comparator; dup, duplicate/copy; e1, excluded at title/abstract screening stage; out, outcome; pop, population; pub, publication

Table 145: Excluded studies at full text review (n=17)

[17] The QoL measure was ineligible, however.

Author, Year	Exclusion rationale in full	Exclusion reason category
Akyol et al., 2019	Guidance document on recommendations of the management of MPS IVA. Bibliography checked. NICE ESA HST submission added to dataset.	Study design not of interest
Bhat et al., 2015	Article discussing perspectives on genetic counselling in India for LSDs. No actual data on costs/resources reported.	No outcome of interest
Bower et al., 2019	Article examining targeted metabolic workup to diagnose inherited metabolic disorders. No cost/resource use outcomes of disease reported.	No outcome of interest
Charrow et al., 2015	Provides recommendations for assessments to manage spinal cord compression in MPS IVA. Although the paper does recommend the frequency of certain assessments, it does not indicate the resource use of particular specialists.	No outcome of interest
Chuang et al., 2017	Reports the cost per sample of NBS with a Bio-Plex immunoassay compared to the cost of NBS with TMS method. However, does not report any costs of treatment.	No outcome of interest
Dabbous et al., 2019	Abstract relating increase in QALY gained with increase in 10-year drug cost, but reports data for a range of orphan drugs (including MPS IV).	Mixed population
Darbà et al., 2019	Review article summarising the submissions made in Spain for ERT, including the Vimizim submission. However, no costs were reported (indicated as N/A).	Study design not of interest
El Moustafa et al., 2017	Assesses performance of GAG analysis for screening of MPS. No cost/resource use data reported.	No outcome of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
Jurecka et al., 2015	Review article. Bibliography checked. Although Burrow et al. 2007 report average per patient cost per year for a 30-40kg individual for ERT and for MPS I, II and VI, there are no data on MPS IV separately. Likewise, Connock et al. 2006 does not report for MPS IV and Hollak et al. 2011 discuss registries in general and not for MPS IVA specifically.	Study design not of interest
Mitchell et al, 2019	Guideline document on recommendations for tonsillectomy, indicating that polysomnography should be performed in children with obstructive sleep-disordered breathing if MPS exhibited. However, no resource use or costs discussed for polysomnography.	No outcome of interest
Nagarajan et al, 2019	Discusses recommendations for intraoperative neurophysiology monitoring during scoliosis surgery in 56 children, 1 of whom was a Morquio patient. Refers to Ney et al. 2013 for a CBA of INM in spinal surgery.	No outcome of interest
Pogue et al, 2018	Table 1 gives annual tx cost per year, apparently, for MPS IV but this appears to be a typo - it is in fact for MPS VI (Maroteaux-Lamy syndrome)	Population not of interest
Ramos Santana et al., 2018	Although this poster presents the average cost for ultra rare diseases for 7 patients in their hospital, the costs for MPS IVA are not reported separately	No outcome of interest
Stapleton et al., 2019	Review of guidance for different types of MPS. Bibliography checked. Refers to NICE submission for ESA (already included from hand-searching NICE website) and to Finnigan et al. 2018 regarding cost-saving from home infusions of ERT (added to dataset).	Study design not of interest

Author, Year	Exclusion rationale in full	Exclusion reason category
Tilles et al., 2013	Reports costs per episode of treating hereditary angiodema attacks	No outcome of interest
Van Gelder et al., 2012	Gives range of costs for treatments of LSDs. Referenced cost paper (Beutler 2006 checked but does not report data for MPS IVA).	Population not of interest
Vartanyan et al., 2018	Review article. Bibliography checked. Reports the same annual cost data given in Puckett 2017 (already included in our SR). Also refers to Ries 2017, but latter reports no cost data.	Study design not of interest

Abbreviations: AB, abstract; CBA, cost-benefit analysis; ERT, enzyme replacement therapy; ESA, elosulfase alfa; FP, full paper; GAG, glycosaminoglycan; HST, highly specialised technologies; INM, intraoperative neurophysiology monitoring; LSD, lysosomal storage disorder; MPS, mucopolysaccharidosis; N/A, non-applicable; NBS, newborn screening; NICE, National Institute of Health and Care Excellence; QALY, quality-adjusted life year; SR, systematic review; TMS, tandem mass spectrometry;

Of the studies excluded during electronic screening or hand-searching (not meeting the eligibility criteria), those worthy of note were:

- Broder et al. 2017 reported costs of HSCT in the USA (HSCT outwith the NICE scope).
- Charrow et al. 2015 made recommendations for assessments to manage spinal cord compression in MPS IVA, including for the frequency of certain assessments. It did not, however, indicate the resource use of particular specialists.
- Chuang et al. 2017 reported the cost per sample for new-born screening (NBS) with a Bio-Plex immunoassay compared to the cost of NBS with tandem mass spectrometry (TMS).
- Finnigan et al. 2016, in an AB-only article, reported how withdrawal of ESA affected six MPS IVA patients and their families in the North-West of England after the NICE decision of 4th June 2015 that ESA was not cost-effective (CE);
- Henkel et al. 2010 in an AB-only article reported the data that would be collected in the Morquio Clinical Assessment Program (MorCAP), including that a Health Resource Utilisation Questionnaire would be used;

- Mitchell et al. 2019 provided a guideline with recommendations for tonsillectomy, including that polysomnography should be performed in children with obstructive sleep-disordered breathing if MPS exhibited. No costs or HCRU were reported, however.
- Nagarajan et al. 2019 discussed recommendations for intraoperative neurophysiology monitoring (INM) during scoliosis surgery in children (including 1 with MPS IVA), referring to a CBA of INM in spinal surgery by Ney et al. 2013.
- Roberts et al. 2017, in an AB-only article, described the Managed Access Agreement (MAA) for ESA, put in place 16th December 2015 for a 5-yr period, by which pts in England can access ESA. Forty-five pts (48% of MPS IVA pts in England) are receiving ESA. Wales and Northern Ireland have also adopted the MAA.
- Rodríguez-López et al. 2017 (AB-only) described early data on cell uptake of recombinant N-acetylgalactosamine-6-sulfatase (GALNS) produced in Pichia pastoris. (ESA, by contrast, is produced in Chinese Hamster Ovary (CHO) cells). They indicate that enzyme produced in P. pastoris may reduce the cost or improve stability/PK/PD attributes compared to enzyme produced in CHO cells and, thus, be useful in ERT for MPS IVA.
- Sivri et al. 2016 describe a newer surgery, hemiepiphysiodesis, for genu valgum. They indicate that it requires a short hospital LOS compared to the traditionally used osteotomy, but the actual data were not reported (AB-only).

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

As per section 17.3.1

17.4.2 The date on which the search was conducted.

As per section 17.3.2

17.4.3 The date span of the search.

As per section 17.3.3

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

As per section 17.3.4

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

As per section 17.3.5

17.4.6 The inclusion and exclusion criteria.

As per section 17.3.6

17.4.7 The data abstraction strategy.

As per section 17.3.7

17.5 Appendix 5: NICE Letter on the Extension of the MAA during the re-evaluation of HST2 for elosulfase alfa

17/11/2020

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Highly Specialised Technology
Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Dear consultees and commentators,

As you will be aware, the Department for Health and Social Care has asked NICE to carry out a Highly Specialised Technology re-evaluation of ID1643 elosulfase alfa (Vimzim).

Please note that following on from advice received from the company this evaluation has been rescheduled. Therefore, we now anticipate that the evaluation will restart in December 2020 when the company will make their submission.

We would also like to provide an update on the managed access agreement on behalf of NICE and NHS England and NHS Improvement.

NICE, NHS England and NHS Improvement (NHSE&I) and BioMarin have reached a commercial agreement which will enable the NICE re-evaluation of elosulfase alfa (Vimzim) to be resumed, following the suspension of this topic in February 2020.

While the re-evaluation continues, we can also confirm that NHSE&I and BioMarin have agreed a commercial arrangement that will ensure patients can continue to access elosulfase alfa over the duration of the NICE re-evaluation (until **December 2021**).

- Because of the interim agreement reached, during this 12-month extension period:
  - Patients receiving elosulfase alfa treatment as part of the Managed Access Agreement (MAA) can continue to receive treatment
  - New patients can start receiving treatment with elosulfase alfa, subject to the criteria outlined in (1) below).

The adaptations to the MAA communicated on 22 July 2020 remain in place until further notice. These adaptations are designed to ensure that no patient is disadvantaged by the impact of COVID-19 (coronavirus) on NHS services.

These include:

1. The MAA baseline assessments for new treatment naïve patients can be deferred until they can be performed safely in hospital on the condition that:

- The patient has a confirmed diagnosis of MPS type IVA as per the diagnosis criteria recommended in Wood et al. (2012), **AND**
- Starting treatment with elosulfase alfa is appropriate in the opinion of the treating clinician.

2. The treating clinician will be responsible for clinical decisions concerning the safe continuation of elosulfase alfa treatment.
3. Routine clinical safety monitoring should continue, however if patients are unable to complete ongoing assessments as required by the MAA (e.g. because circumstances do not allow), these should be deferred until they can be performed safely under valid, standardised conditions.
4. The 6-monthly patient caseload review **will not** be performed, however if clinical teams would like to seek advice from the Managed Access Oversight Committee on individual cases they are advised to contact managed.access@nice.nhs.uk to coordinate a response. **Please do not include any patient identifiable information in any correspondence to NICE, use the managed access identifier only.**
5. The treatment stopping criteria for missed treatments (missing 3 infusions in a 14-month period and/or failing to perform the managed access clinical and quality of life assessments) will continue to be flexed to take account of each patient's personal circumstances during this period.
6. It is recommended that elosulfase alfa dose adjustments are not considered unless weight can be measured under standardised conditions.

Patients and their families should be advised to contact their clinical team if they have any concerns about their treatment while these measures are in place.

NICE and NHSE&I will provide a further update to stakeholders concerning the schedule for the NICE re-evaluation and details on the terms that will be applied during the interim extension period.

Kind regards

Jasdeep Hayre

Associate Director, Technology Appraisals & HST

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (https://www.nice.org.uk/about/who-we-are/policies-and-procedures/nice-equality-scheme).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Clarification questions

February 2021

File name	Version	Contains confidential information	Date
ID1643 clarification letter from ERG 150121 [ACIC]_v4_22022021 _REDACTED	ACIC_v4_REDACTED	Yes – Redacted	22/02/2021

Tables of figures

Table of tables

Section A: Clarification on effectiveness data

The ERG has assumed that MorCAP and MOR-001 are the same natural history study and has used MOR-001 throughout the clarification questions to refer to the natural history study. Additionally, for the questions relating to matching of patients from MOR-001, the ERG requests that the company uses the full population from MOR-001 and not the subset referred to in the submission matched to MOR-005.

Matching adjusted analysis

A1. Priority Question: Please conduct a propensity score matching (PSM) analysis matching patients in MOR-001 (MorCAP) to the ex-trial patients in the MAA to enable a matching adjusted analysis of elosulfase alfa with placebo that uses the full 10 years of data on elosulfase alfa from the ex-trial patients (using the baseline at the start of the original study, i.e. baseline prior to starting elosulfase for ex-trial patients resulting in approximately 10 years of follow-up). Please match the MOR-001 patients to the MAA ex-trial patients and present:

a) **the resulting matched population baseline characteristics for each treatment group (MAA ex-trial matched patients and MOR-001 patients);**
b) **the results for all outcomes detailed in question A3; and**
c) **the results for all outcomes detailed in question A4.**

[redacted]

A2. Priority Question: Please conduct a PSM analysis to estimate comparative data for elosulfase alfa available from the ex-trial patients in the MAA for the full 10 years of follow up available from MOR-001. The ERG advises that this could be in the following steps:

- **Using the MAA ex-trial patients as the "baseline" population, match the MAA treatment-naive patients to this "baseline" population to estimate results for the first three years of treatment with elosulfase alfa.**
- **Three years MAA treatment-naive patients (PSM adjusted) + 7 years of MAA ex-trial patients. Together this should provide 10 years of results for elosulfase alfa (please refer to Questions A3 and A4 for results).**
- **For the "untreated" population, match the MOR-001 (MorCAP) patients to the "baseline" population (effectively the MAA ex-trial patients). This should**

provide a comparable patient population to the elosulfase treated population for 10 years of results (please refer to Questions A3 and A4 for results).

- **Please provide the resulting matched population baseline characteristics for each treatment group (elosulfase alfa and placebo).**

[redacted]

A3. Priority question: Please present the results for the elosulfase-treated population and the untreated population after the propensity score matching, as described in questions A1 and A2. Additionally, please report baseline characteristics and net effective sample size for each population:

a) **wheelchair use change from baseline for each baseline category of wheelchair use;**
b) **FVC change from baseline;**
c) **6-minute walking test change (6MWT) from baseline;**
d) **FEV1 change from baseline; and**
e) **urinary keratan sulfate change from baseline.**

[redacted]

A4. Priority question. For the matched ex-trial MAA population described in questions A1 and A2, please provide the following outcomes:

a) **Change in wheelchair use by year, for each baseline category of wheelchair use;**
b) **FVC change by year;**
c) **6MWT change by year; and**
d) **Time to surgery and type of surgery.**

[redacted]

A5. Priority Question: Please conduct a PSM analysis matching patients in MOR-001 (MorCAP) to the elosulfase alfa patients in MOR-005 who received elosulfase alfa 2.0mg/kg QW (and who also received this dose of elosulfase alfa in MOR-004; N=56) using the baseline from the start of MOR-004 (i.e. prior to start of treatment with

elosulfase) to enable a matching adjusted analysis of elosulfase alfa with placebo. Please match the MOR-001 patients to the MOR-005 patients (N=56) and present:

a) **the resulting matched population baseline characteristics for each treatment group (MOR-005 matched patients and MOR-001 patients);**
b) **the results for all outcomes detailed in question A12; and**
c) **the results for all outcomes detailed in question A13.**

[redacted]

Study methods

A6. Priority question: Please provide details of the matching process used to derive the matched population from MOR-001 for the comparison with MOR-005 presented in the CS.

[redacted]

A7. Please provide details of the method of randomisation and if applicable, the method of allocation concealment for the following studies:

a) MOR-004; and
b) MOR-005.

In MOR-004, subjects who met the study entry criteria were randomised (1:1:1) to one of three treatment groups using the interactive web or voice response system: (1) placebo, (2) elosulfase alfa 2.0 mg/kg/qow with placebo infusions alternate weeks, or (3) elosulfase alfa 2.0 mg/kg/week for 24 consecutive weeks. Randomisation was stratified by screening 6MWT categories (≤200 meters and >200 meters) and age group (5-11, 12-18, and ≥19 years old) (BioMarin, 2013).

The randomisation schedule was developed by an independent third party to ensure that BioMarin and site personnel were blinded to treatment assignment. In addition, an internal unblinded BioMarin team member not directly involved with the study verified all treatment assignments made by the interactive web-response prior to dosing to ensure all subjects received the appropriate treatment (BioMarin, 2013).

In MOR-005, subjects who met the inclusion and exclusion criteria and were previously assigned in MOR-004 to either 2.0 mg/kg/qw or 2.0 mg/kg/qow elosulfase alfa were maintained on that dose regimen upon entering MOR-005. Subjects who were previously randomised to placebo in MOR-004 were re-randomised 1:1 to either 2.0 mg/kg/qw or 2.0 mg/kg/qow elosulfase alfa. An Interactive Voice Response System (IVRS) was utilised as well as the randomisation schedule developed by an independent third-party vendor so that BioMarin and site personnel were blind to treatment assignment (BioMarin, 2017). After analysis of the final primary efficacy and safety results in MOR-004 and based on the recommendation of the Data Monitoring Committee (DMC), the dose for Part 2 of MOR-005 (2.0 mg/kg/qw) was determined. In Part 2, all subjects received 2.0 mg/kg/qw. The specific time of transition for each subject depended on date of study enrolment, ranging from Week 39 to Week 96.

MOR-004 was a double-blind study where treatment assignment was unknown to study subjects, Investigators, site personnel, BioMarin and its designees. Elosulfase alfa and placebo were identical in appearance and placebo solution consisted of the same excipients as the elosulfase alfa solution. The study drug was labelled with study number and unique identification number. An internal unblinded BioMarin team member not directly involved with the study verified all treatment assignments prior to dosing to ensure all subjects received the appropriate treatment. There was no unscheduled unblinding during the study (BioMarin, 2013).

After MOR-004 was unblinded for final primary efficacy analysis, BioMarin was unblinded to assigned treatment in MOR-005; however, subjects, Investigators, and site personnel remained blind to subject treatment assignment until the optimal elosulfase alfa dosing regimen was determined (BioMarin, 2013).

A8. Please provide the definitions of the following populations in the MOR-005 study:

a) ITT population (or mITT if applicable);
b) per protocol population; and
c) MPP population.

ITT was defined as all subjects who were enrolled into the parent MOR-004 trial and continued into MOR-005 and who received at least one dose of elosulfase alfa, while the per-protocol (PP) population excludes all the patients who were excluded from the MOR-004 PP population, and is defined as the subset of patients who were compliant with the protocol as indicated in the statistical analytical plan (BioMarin, 2017).

Although surgeries were not allowed during MOR-004, due to the long-term nature of the extension study, they could not reasonably be prohibited during MOR-005. However, endurance test results can be impacted by the occurrence of orthopaedic surgery and the subsequent recovery period. Therefore, the PP population for analysis excluded data on or after orthopaedic surgery, as well as 24-week intervals of data where ≥3 infusions were missed and all data subsequent to such intervals (BioMarin, 2017).

The PP population was previously used to perform sensitivity analyses for the efficacy endpoints in Part I. However, at a Steering Committee Investigator meeting on February 8, 2015 in Orlando, FL, USA, where analyses of Week 120 data was presented, study investigators determined that the pre-specified PP population was unnecessarily restrictive and excluded too many patients (95 patients excluded; 51 patients due to missing ≥3 infusions) and therefore, the modified per-protocol (MPP) population was established. The MPP population excluded patients who underwent orthopaedic surgery during the study (n=38) and/or exhibited recurrent noncompliance with the study protocol. Missed infusions were used as an indicator of compliance; patients missing ≥20% of their scheduled elosulfase alfa infusions during MOR-005 were identified as noncompliant (n=14). In total, 49 patients were excluded, thereby allowing inclusion of an additional 46 patients as compared to the PP population (BioMarin, 2017).

A9. Please can the company:

a) clarify the planned duration of follow-up of patients completing MOR-005 taking into account follow-up from MOR-004; in Table 4 of the CS it is described as 240 weeks but elsewhere it is reported as 120 weeks.

b) provide the mean and standard deviation for duration of follow-up of the 56 patients in the elosulfase alfa 2.0mg/kg qw arm of MOR-005 (and who also received this dose of elosulfase alfa in MOR-004) inclusive of the follow-up from MOR-004;

c) provide the median and range for duration of follow-up of the 56 patients in the elosulfase alfa 2.0mg/kg qw arm of MOR-005 (and who also received this dose of elosulfase alfa in MOR-004) inclusive of the follow-up from MOR-004.

The planned follow-up duration for MOR-005 was up to 240 weeks (plus the 24 weeks from the MOR-004 parent study, totalling to 264 weeks of follow-up). However, none of the patients completed the 140 weeks of MOR-005 as they switched to commercially available therapy. Therefore, all analyses from MOR-005 presented in the CS and the publications are

based on week 120 follow-up since all patients had the opportunity to complete at least 120 weeks of the study. After 120 weeks, there was considerable drop-out, as many patients switched to commercial therapy, limiting the amount of data collected.

Mean (SD)= 147.6 (36.83)

Median= 141.3

Min, max= 34.1, 243.1

A10. Please provide the statistical analysis plan for MOR-004.

The statistical analysis plan for MOR-004 has been included in the additional materials provided.

Baseline characteristics

A11. Priority question: Please provide baseline patient characteristics (including age, FVC, FEV1, wheelchair use, 6MWT, 3MSCT, and urinary keratin sulphate) for each treatment arm in the following studies and subgroups:

a) **All patients in MOR-004 split by treatment arm;**

b) **All patients in MOR-005 split by treatment arm;**

c) **The subgroup of treatment naive patients in the MAA study;**

d) **The subgroup of ex-trial patients in the MAA study;**

e) **The subgroup of ex-trial patients in the MAA study, using the baseline as the patients baseline from the point of entry into their first elosulfase alfa trial;**

f) **The subgroup of ex-trial patients in the MAA study who have only ever received the elosulfase alfa 2mg/kg qw dose regimen, using the baseline as their point of entry into their first elosulfase alfa trial;**

g) **All patients in MOR-001; and**

h) **Patients in MOR-001 after matching to patients in MOR-005.**

Baseline patient characteristics for MOR-004, MOR-005, the MAA, MOR-001, and patients in MOR-001 after matching to patients in MOR-005 elosulfase 2.0 mg/kg QW arm (the licensed dose) have been provided in the tables below, split by treatment arm.

As communicated previously to the ERG, analyses on wheelchair use were conducted post-hoc and these have been added to the relevant tables below.

Table 1: MOR-004 baseline characteristics

MOR-004 at baseline (BioMarin, 2013)			
	Placebo (n=59)	Elosulfase alfa 2.0 mg/kg/qow (n=59)	Elosulfase alfa 2.0 mg/kg/week (n=58)
Age (years)			
Mean (SD)	15.0 (11.30)	15.3 (10.79)	13.1 (8.10)
Median	11.9	12.0	11.1
Min, Max	5, 57	5, 49	5, 42
FVC, L			
Mean (SD)	1.2 (0.85)	1.1 (0.65)	0.9 (0.50)
Median	0.9	0.9	0.8
Min, Max	0.3, 5.0	0.3, 3.0	0.3, 3.0
FEV1, L			
Mean (SD)	1.0 (0.69)	0.9 (0.52)	0.8 (0.42)
Median	0.8	0.8	0.7
Min, Max	0.3, 3.8	0.3, 2.6	0.3, 2.5
6MWT (meters)			
Mean (SD)	211.9 (69.88)	205.7 (81.19)	203.9 (76.32)
Median	228.9	218.0	216.5
Min, Max	36, 312	47, 320	42, 322
3MSCT (stairs/minute)			
N (for 3MSCT only)	11	16	9
Mean (SD)	30.0 (14.05)	27.1 (15.80)	29.6 (16.44)
Median	30.8	25.5	30.5
Min, Max	0, 59	0, 67	0, 72
Normalised urinary keratin sulphate* (ug/mg)			
Mean (SD)	25.7 (15.09)	28.6 (21.17)	26.9 (14.11)

Median	26.7	27.4	24.1
Min, Max	2, 53	2, 117	2, 59
Wheelchair use			
n	[redacted]	[redacted]	[redacted]
No use	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Some use	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Always use	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Yes – not specified	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)

*Calculated as urine keratin sulphate divided by urine creatinine

Table 2: Baseline characteristics MOR-005 ITT population

MOR-005: ITT population – at MOR-005 week 0 (BioMarin, 2017)					
	PBO-QOW* (n=29)	PBO-QW* (n=29)	QOW-QOW* (n=59)	QW-QW* (n=56)	Total (n=173)
Age (years)					
Mean (SD)	16.7 (13.66)	13.5 (8.50)	15.3 (10.79)	12.8 (8.01)	14.4 (10.20)
Median	11.1	11.9	12.0	10.6	11.7
Min, Max	5 , 57	5 , 33	5 , 49	5 , 42	5 , 57
FVC, L					
Mean (SD)	1.2 (0.81)	1.1 (0.97)	1.1 (0.67)	1.0 (0.51)	1.1 (0.70)
Median	0.9	0.8	0.9	0.8	0.9
Min, Max	0.4 , 3.4	0.4 , 5.2	0.4 , 3.2	0.3 , 2.9	0.3 , 5.2
FEV1, L					
Mean (SD)	1.1 (0.65)	0.9 (0.78)	1.0 (0.55)	0.9 (0.42)	0.9 (0.57)
Median	0.8	0.6	0.9	0.7	0.8
Min, Max	0.3 , 2.6	0.3 , 4.1	0.3 , 2.7	0.3 , 2.4	0.3 , 4.1
6MWT (meters)					
Mean (SD)	243.5 (93.18)	212.2 (66.30)	220.5 (88.24)	246.6 (80.51)	231.5 (83.81)
Median	252.1	225.4	238.1	251.9	239.4
Min, Max	74.3 , 501.0	50.6 , 335.0	44.1 , 370.4	52.0 , 399.9	44.1 , 501.0

3MSCT (stairs/minute)					
Mean (SD)	37.7 (20.84)	29.8 (15.16)	30.6 (17.85)	34.7 (18.50)	33.0 (18.27)
Median	35.5	28.8	28.6	34.1	31.9
Min, Max	0.0 , 79.3	0.0 , 63.7	0.2 , 75.0	0.0 , 82.3	0.0 , 82.3
Normalised urinary keratin sulphate (µg/mg)**					
Mean (SD)	23.5 (14.22)	25.2 (13.10)	16.4 (10.01)	14.3 (8.43)	18.4 (11.65)
Median	26.0	26.4	14.6	13.8	16.2
Min, Max	3.5 , 49.9	2.2 , 49.3	2.0 , 50.6	0.7 , 37.6	0.7 , 50.6
Wheelchair use					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No use	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Some use	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Always use	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Yes – not specified	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)

*PBO-QOW, Placebo-elosulfase alpha 2.0 mg/kg/qow; PBO-QW, Placebo- elosulfase alpha 2.0 mg/kg/qw; QOW-QOW, elosulfase alpha- elosulfase alpha 2.0 mg/kg/qow; QW-QW, elosulfase alpha- elosulfase alpha 2.0 mg/kg/qw.
**Calculated as urine keratin sulphate divided by urine creatinine

Table 3: MAA baseline characteristics

MAA at baseline (BioMarin data on file, 2021)				
	Ex-Trial Patients (n=[redacted]) – At baseline of clinical trial	Ex-Trial Patients - At MAA Enrolment (n=[redacted])	Ex-trial Patients only received licensed dose (n=[redacted]) – At baseline of clinical trial	ERT-Naïve Patients (n=[redacted]) – At MAA enrolment
Age (years)				
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]

FVC, L				
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
FEV1, L				
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
6MWT (meters)				
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
3MSCT (stairs/minute)				
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Normalised urinary keratin sulphate* (ug/mg)				
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]	[redacted], [redacted]
Wheelchair use (n, as % of patient cohort)				

No Use Wheelchair	n= [redacted], [redacted]%	n= [redacted], [redacted]%	n= [redacted], [redacted]%	n= [redacted], [redacted]%
Sometimes Use Wheelchair	n= [redacted], [redacted]%	n= [redacted], [redacted]%	n= [redacted], [redacted]%	n= [redacted], [redacted]%
Wheelchair dependent	n= [redacted], [redacted]%	n= [redacted], [redacted]%	n= [redacted], [redacted]%	n= [redacted], [redacted]%

*Calculated as urine keratin sulphate divided by urine creatinine

Table 4: MOR-001 baseline characteristics

MOR-001 at baseline (Harmatz et al., 2013)	
	All patients (n=325)
Age (years)	
Mean	14.5
Median	11.6
Min, Max	1.1, 65.6
FVC, L	
n	261
Mean (SD)	1.2 (0.9)
Median	0.9
Min, Max	0.5, 5.0
FEV1, L	
Mean (SD)	Outcome not collected in MOR-001
Median	Outcome not collected in MOR-001
Min, Max	Outcome not collected in MOR-001
6MWT (meters)	
n	316
Mean (SD)	212.6 (152.2)
Median	224.0
Min, Max	0, 864

3MSCT (stairs/minute)	
n	274
Mean (SD)	30.0 (24.0)
Median	29.0
Min, Max	0.0, 115.0
Normalised urinary keratin sulphate* (ug/mg)	
n	310
Mean (SD)	36.4 (28.4)
Median	31.20
Min, Max	0.9, 222.7
Wheelchair use, n (%)	
No use	[redacted]
Some use	[redacted] ([redacted]%)
Always use	[redacted] ([redacted]%)
Yes – not specified	[redacted] ([redacted]%)

*Calculated as urine keratin sulphate divided by urine creatinine
SOURCE: (Harmatz et al., 2013)

Table 5: Baseline characteristics of MOR-001 matched to MOR-005

MOR-001 matched to MOR-005 (at baseline)	
	Matched patients (n=79)
Age (years)	
Mean	17.8 ± 13.0
Median	12.0
Min, Max	5.0, 65.0
FVC, L	
n	74
Mean (SD)	1.2 (0.7)
Median	Not reported
Min, Max	Not reported
FEV1, L	

n	74
Mean (SD)	1.0 (0.6)
Median	Not reported
Min, Max	Not reported
6MWT (meters)	
Mean (SD)	210.4 (83.4)
Median	221.5
Min, Max	30.0, 325.0
3MSCT (stairs/minute)	
n	74
Mean (SD)	32.2 (17.8)
Median	30.6
Min, Max	0.0, 85.6
Normalised urinary keratin sulphate* (ug/mg)	
Mean (SD)	32.2 (27.4)
Median	27.6
Min, Max	2.3, 168.1
Wheelchair use	
No use	[redacted]
Some use	[redacted] ([redacted]%)
Always use	[redacted] ([redacted]%)
Yes – not specified	[redacted] ([redacted]%)

*Calculated as urine keratin sulphate divided by urine creatinine
SOURCE: (Hendriksz et al., 2016a, Hendriksz et al., 2016b)

Outcomes

A12. Priority question: Please provide the results for all outcomes of relevance to the NICE final scope for:

a) the full trial population from MOR-001; and

b) the matched population from MOR-001 detailed in the CS as used in the comparison with MOR-005.

Data from 1- and 2-year longitudinal analysis of MOR-001 for endurance and pulmonary outcomes are presented in the table below (Hendriksz et al., 2015).

Mean baseline 6MWT distances for the subjects analysed in this study were at least 2- to 3-fold below the lower limits of age-specific normal ranges reported for healthy children and adolescents (Geiger et al., 2007, Lammers et al., 2008, Li et al., 2007, Ulrich et al., 2013) and for healthy adults (2002, Chetta et al., 2006): one study reported a mean 6MWT distance of 470 ± 59 m for healthy boys and girls aged 4–11 years (Lammers et al., 2008), while another reported a mean 6MWT distance of 618 ± 79 m for healthy children and adolescents aged 5–17 years (Ulrich et al., 2013); for adults, mean 6MWT distances of 593 ± 57 m and 638 ± 44 m have been reported for healthy women and men, respectively (Chetta et al., 2006). A general decline in 6MWT distance from baseline was observed across all subjects over the course of this 2-year longitudinal study, indicating that Morquio A syndrome is characterised by progressive impairment in endurance and mobility. Patient quality of life is expected to worsen as mobility declines and wheelchair dependence increases. A similar change in 3MSCT was not observed, likely due to the fact that this test may not be suitable for Morquio A patients, who typically have severe skeletal dysplasia, short stature and joint involvement that considerably limit the ability to climb stairs. Difficulties with standardising stair height and stairwell configuration may have also influenced the data.

Patients also showed significant impairment in respiratory function at baseline, with absolute FVC and MVV volumes comparable to those reported for other MPS disorders (Lin et al., 2014, Swiedler et al., 2005, Muenzer et al., 2006) and well below those reported for healthy subjects of normal stature (Bjure, 1963, Hankinson et al., 1999, Rosenthal et al., 1993).

As communicated previously to the ERG, analyses for FEV1, wheelchair use, and MPS HAQ were conducted post-hoc and these have been added in the table below.

Table 6: MOR-001 outcomes

Outcome	With year 1 follow-up	With year 2 follow-up

6MWT (meters)		
N	[redacted]	[redacted]
Mean (SD) baseline	[redacted] ([redacted])	[redacted] ([redacted])
Least square mean (SE) change from baseline	[redacted] ([redacted])	[redacted] ([redacted])
Annualised change (SE), all subjects	[redacted] ([redacted])	
3MSCT (steps/min)		
N	[redacted]	[redacted]
Mean (SD) baseline	[redacted] ([redacted])	[redacted] ([redacted])
Least square mean (SE) change from baseline	[redacted] ([redacted])	[redacted] ([redacted])
Annualised change (SE), all subjects	[redacted] ([redacted])	
FVC (L)		
N	[redacted]	[redacted]
Mean (SD) baseline	[redacted] ([redacted])	[redacted] ([redacted])
Least square mean (SE) change from baseline	[redacted] ([redacted])	[redacted] ([redacted])
Annualised change (SE), all subjects	[redacted] ([redacted])	
MVV (L/min)		
N	[redacted]	[redacted]
Mean (SD) baseline	[redacted] ([redacted])	[redacted] ([redacted])
Least square mean (SE) change from baseline	[redacted] ([redacted])	[redacted] ([redacted])
Annualised change (SE), all subjects	[redacted] ([redacted])	
FEV1 (L)		
N	[redacted]	[redacted]
Mean (SD) baseline	[redacted] ([redacted])	[redacted] ([redacted])

Least square mean (SE) change from baseline		[redacted] ([redacted])	[redacted] ([redacted])
MPS HAQ self-care domain score			
N		[redacted]	[redacted]
Mean (SD) baseline		[redacted] ([redacted])	[redacted] ([redacted])
Least square mean (SE) change from baseline		[redacted] ([redacted])	[redacted] ([redacted])
MPS HAQ mobility domain score			
N		[redacted]	[redacted]
Mean (SD) baseline		[redacted] ([redacted])	[redacted] ([redacted])
Least square mean (SE) change from baseline		[redacted] ([redacted])	[redacted] ([redacted])
MPS HAQ caregiver assistance domain score			
N		[redacted]	[redacted]
Mean (SD) baseline		[redacted] ([redacted])	[redacted] ([redacted])
Least square mean (SE) change from baseline		[redacted] ([redacted])	[redacted] ([redacted])
Wheelchair use, n (%)			
Baseline	No use	[redacted] ([redacted])	[redacted] ([redacted])
	Some use	[redacted] ([redacted])	[redacted] ([redacted])
	Always use	[redacted] ([redacted])	[redacted] ([redacted])
No use		[redacted] ([redacted])	[redacted] ([redacted])
Some use		[redacted] ([redacted])	[redacted] ([redacted])
Always use		[redacted] ([redacted])	[redacted] ([redacted])

SOURCE: (Harmatz et al., 2015)

The subset of MOR-001 (MorCAP) patients meeting the following criteria: ≥5 years of age and average 6MWT distance ≥30 and ≤325 m at baseline, for whom longitudinal data (Year

1 and/or Year 2 follow-up) were available, were used to establish an untreated subpopulation comparable to the MOR-005 ITT population. As explained in question A8, endurance test results can be impacted by the occurrence of orthopaedic surgery and the subsequent recovery period, and therefore, an MPP population in MOR-005 was established that excluded patients who underwent orthopaedic surgery during the study period. To enable comparisons to the MOR-005 MPP population, MorCAP was further restricted to exclude patients who underwent orthopaedic surgery within the 3 months prior to the time at which their baseline data were collected or during the subsequent 2-year period.

LS mean change from baseline results for 6MWT, 3MSCT, uKS, FVC, FEV1, and MPS HAQ from the MOR-005 elosuflase alpha QW arm (MPP population) compared with data from the corresponding untreated patients from the MorCAP natural history study are presented in the table below.

Table 7: MOR-001 matched to MOR-005 outcomes

Outcome	**Year 1[a]**		**Year 2[b]**	
	MOR-001 (MorCAP) matched population	MOR-005 elosuflase alpha QW arm - MPP	MOR-001 (MorCAP) matched population	MOR-005 elosuflase alpha QW arm - MPP
6MWT				
N	67	43	27	41
LS mean change from baseline[c] (SE)[d]	-6.7 (8.78)	38.5 (11.02)	-21.9 (12.30)	39.0 (11.32)
p-value[e] for difference from MorCAP		**0.0016**		**0.0003**
3MSCT				
N	67	43	27	41
LS mean change from baseline[c] (SE)[d]	0.5 (1.51)	5.5 (1.85)	-1.2 (2.39)	6.2 (2.24)
p-value[e] for difference from MorCAP		**0.0375**		**0.0236**
uKS				
N	59	41	13	38
LS mean change from baseline[c] (SE)[d]	29.6 (9.30)	-57.5 (11.16)	6.2 (8.46)	-63.8 (7.47)
p-value[e] for difference from MorCAP		**<0.0001**		**<0.0001**
FVC, L				
N	63	41	25	36
LS mean (SE)	1.1129 (0.02)	1.1547 (0.03)	1.0881 (0.06)	1.1223 (0.05)
LS mean change from baseline (SE)	0.0103 (0.02)	0.0521 (0.03)	-0.0145 (0.06)	0.0197 (0.05)
p-value		0.2938		0.6710
FEV1, L				
N	63	41	24	37
LS mean (SE)	0.9528 (0.03)	0.9980 (0.03)	0.9374 (0.05)	0.9705 (0.05)

LS mean change from baseline (SE)	-0.0310 (0.03)	0.0142 (0.03)	-0.0464 (0.05)	-0.0133 (0.05)
p-value		0.2817		0.6588
MPS HAQ				
Caregiver assistance domain				
N	67	43	25	43
LS mean (SE)	25.7 (0.5)	23.7 (0.09)	26.1 (0.8)	24.0 (0.9)
LS mean change from baseline (SE)	−0.7 (0.6)	-2.6 (1.1)	-0.3 (0.9)	-2.3 (1.1)
p-value	0.2727	**0.0209**	0.7734	**0.0387**
Mobility domain				
N	67	43	26	43
LS mean	4.3 (0.2)	3.4 (0.2)	4.9 (0.3)	3.5 (0.2)
LS mean change from baseline	-0.5 (0.2)	-0.8 (0.3)	0.1 (0.3)	-0.7 (0.3)
p-value	**0.0469**	**0.0018**	0.6861	**0.0111**
Self-care domain				
N	67	43	26	43
LS mean	3.0 (0.1)	2.8 (0.2)	3.2 (0.2)	2.6 (0.2)
LS mean change from baseline	-0.0 (0.2)	-0.7 (0.2)	0.2 (0.2)	-0.8 (0.2)
p-value	0.9140	**0.0009**	0.3840	**<0.0001**

SOURCE: (Hendriksz et al., 2016a, Hendriksz et al., 2016b, Hendriksz, 2017)
[a] Year 1 represents data collected from the MOR-004/005 Week 72 assessment and the MorCAP Year 1 follow-up window.
[b] Year 2 represents data collected from the MOR-004/005Week 120 assessment and the MorCAP Year 2 follow-up.
[c] Baseline LS means are based on ANCOVA of baseline measurement with model terms treatment age group, and 6MWT distance category.
[d] LS mean changes based on repeated measures ANCOVA model including treatment, time point, treatment and time point interaction, age group, and baseline measurement
[e] P-value determined by t-test and the repeated measures ANCOVA model.

For completeness, data from the publication on pulmonary outcomes (FVC and FEV1) from the MOR-005 entire MPP population compared with data from the corresponding untreated patients from the MorCAP natural history study has also been presented (please see table below).

Table 8: Pulmonary outcomes of MOR-001 matched to MOR-005 (MPP)

Outcome	**Year 1[a]**		**Year 2[b]**	
	MOR-001 matched population	MOR-005 MPP population	MOR-001 matched population	MOR-005 MPP population
FVC, L				
N	63	117	25	111
LS mean change from baseline	0.0008	0.0589	-0.0299	0.0827
p-value for difference from MorCAP		**0.0279**		**0.0429**
FEV1, L				
N	63	117	24	112

LS mean change from baseline	-0.0399	0.0385	-0.052	0.06
p-value for difference from MorCAP		**0.0079**		**0.0339**

A repeated measure analysis of covariance (ANCOVA) model was used to compare least square mean (LS mean) changes from baseline at year 1 and 2 of the MOR-005 MPP and MorCAP populations. The model included treatment, time point, baseline height, treatment and time point interaction, age group, and baseline measurement
Source: (Harmatz et al., 2015)

A13. Please provide details of the number of patients undergoing surgery and a breakdown of the type of surgery received by patients, split by treatment arm for the following studies:

a) MOR-004;
b) MOR-005;
c) MAA; and
d) MOR-001.

The MOR-004 trial excluded patients who had major surgery within 3 months before study entry or planned major surgery during the 24-week study treatment period. No patient underwent surgery during the study period as per protocol.

During the MAA, although patients could receive surgical interventions, this data was not collected. This is one of the limitations of the MAA as acknowledged in the CS (p 264).

The number of patients who underwent surgery in MOR-005 and MOR-001 during the study period are provided in the tables below, including a breakdown of the type of surgery received by patients.

Table 9: MOR-005 surgery incidence per type of surgery

	MOR-005: safety population (BioMarin, 2017)									
	PBO-QOW* (n=29)		PBO-QW* (n=29)		QOW-QOW* (n=59)		QW-QW* (n=56)		Total (n=173)	
	Incidence[a]	**Event[b]**	**Incidence[a]**	**Event[b]**	**Incidence[a]**	**Event[b]**	**Incidence[a]**	**Event[b]**	**Incidence[a]**	**Event[b]**
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Central venous catheterisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth extraction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical device implantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Astringent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Circumcision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dental disorder prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear tube insertion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical device removal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal decompression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal fusion surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Catheter placement	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Cerumen removal	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Epiphyseal stapling	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Gastrostomy	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Knee operation	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Myringotomy	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Skin lesion excision	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Surgery	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Tooth repair	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Tracheostomy	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Wisdom teeth removal	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]
Wound drainage	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]	[redacted] ([redacted]%)	[redacted]

*PBO-QOW, Placebo-elosulfase alpha 2.0 mg/kg/qow; PBO-QW, Placebo- elosulfase alpha 2.0 mg/kg/qw; QOW-QOW, elosulfase alpha- elosulfase alpha 2.0 mg/kg/qow; QW-QW, elosulfase alpha- elosulfase alpha 2.0 mg/kg/qw.

[a] Subjects who experienced more than 1 surgery were counted once for incidence

[b] Multiple events were counted if a subject had the same surgery with different onset dates or times

Table 10: MOR-001 surgery incidence per type of surgery

	MOR-001 (n = 353) (BioMarin data on file, 2021)	
Surgery	**Event[a]**	**Incidence[b]**
Ear tube insertion	[redacted]	[redacted] ([redacted]%)
Osteotomy	[redacted]	[redacted] ([redacted]%)
Adenoidectomy	[redacted]	[redacted] ([redacted]%)
Spinal fusion surgery	[redacted]	[redacted] ([redacted]%)
Medical device removal	[redacted]	[redacted] ([redacted]%)
Spinal decompression	[redacted]	[redacted] ([redacted]%)
Epiphyseal surgery	[redacted]	[redacted] ([redacted]%)
Tonsillectomy	[redacted]	[redacted] ([redacted]%)
Spinal support	[redacted]	[redacted] ([redacted]%)
Hip surgery	[redacted]	[redacted] ([redacted]%)
Spinal laminectomy	[redacted]	[redacted] ([redacted]%)
Hip arthroplasty	[redacted]	[redacted] ([redacted]%)

Bone graft	[redacted]	[redacted] ([redacted]%)
Knee operation	[redacted]	[redacted] ([redacted]%)
Arthrodesis	[redacted]	[redacted] ([redacted]%)
Myringotomy	[redacted]	[redacted] ([redacted]%)
Medical device implantation	[redacted]	[redacted] ([redacted]%)
Orthopedic procedure	[redacted]	[redacted] ([redacted]%)
Circumcision	[redacted]	[redacted] ([redacted]%)
Inguinal hernia repair	[redacted]	[redacted] ([redacted]%)
Spinal operation	[redacted]	[redacted] ([redacted]%)
Tooth extraction	[redacted]	[redacted] ([redacted]%)
Epiphyseal stapling	[redacted]	[redacted] ([redacted]%)
Joint stabilisation	[redacted]	[redacted] ([redacted]%)
Adenotonsillectomy	[redacted]	[redacted] ([redacted]%)
Bone operation	[redacted]	[redacted] ([redacted]%)
Tracheostomy	[redacted]	[redacted] ([redacted]%)

Umbilical hernia repair	[redacted]	[redacted] ([redacted]%)
Ear tube removal	[redacted]	[redacted] ([redacted]%)
Joint surgery	[redacted]	[redacted] ([redacted]%)
Knee arthroplasty	[redacted]	[redacted] ([redacted]%)

[a] Multiple events were counted if a subject had the same Surgery with different onset dates or times

[b] Subjects who experienced more than 1 Surgery were counted once for incidence

A14. Priority question: Please provide the following change from baseline outcome data for the ITT population of the elosulfase alfa 2.0mg/kg qw arm of MOR-005 (and who also received this dose of elosulfase alfa in MOR-004; n=56) using the baseline from the start of MOR-004 (i.e. prior to start of treatment with elosulfase):

a) **3MSCT;**
b) **6MWT;**
c) **wheelchair use;**
d) **FVC;**
e) **FEV1;**
f) **mortality;**
g) **HRQoL; and**
h) **urinary keratin sulfate.**

The change in baseline data for the ITT population of the elosulfase alfa 2.0mg/kg qw arm of MOR-005 trial using the baseline from the start of MOR-004 has been provided in the tables below. As no patient died during the MOR-004 and MOR-005 trials, analyses on change in baseline for mortality have not been conducted.

Table 11: Change from baseline outcome data in MOR-005 ITT population

Outcome	Elosulfase alpha 2.0mg/kg QW (n=58)**
6MWT (meters): Change from Baseline to Week 24 (MOR-005 Week 0)	
n	57
Mean (SD)	36.5 (58.49)
Median	20.0
Min , Max	-57.8 , 228.7
6MWT (meters): Change from Baseline to Week 36 (MOR-005 Week 12)	
n	54
Mean (SD)	42.2 (52.13)
Median	41.7
Min , Max	-61.5 , 228.9
6MWT (meters): Change from Baseline to Week 48 (MOR-005 Week 24)	
n*	26
Mean (SD)	33.4 (64.89)
Median	32.3
Min , Max	-120.0 , 181.5
6MWT (meters): Change from Baseline to Week 72 (MOR-005 Week 48)	
n	55
Mean (SD)	30.6 (73.66)
Median	32.0
Min , Max	-149.4 , 229.3
6MWT (meters): Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	[redacted] ([redacted])
Median	[redacted]
Min , Max	[redacted] ([redacted])
3MSCT (stairs/min): Change from Baseline to Week 24 (MOR-005 Week 0)	
n	57
Mean (SD)	4.8 (8.06)
Median	4.3
Min , Max	-12.4, 20.5
3MSCT (stairs/min): Change from Baseline to Week 36 (MOR-005 Week 12)	
n	54
Mean (SD)	6.1 (8.43)
Median	4.5
Min , Max	-16.2, 27.2
3MSCT (stairs/min): Change from Baseline to Week 48 (MOR-005 Week 24)	
n*	26
Mean (SD)	7.7 (11.02)
Median	4.4
Min , Max	22.0 , 30.4
3MSCT (stairs/min): Change from Baseline to Week 72 (MOR-005 Week 48)	
n	54

Mean (SD)	5.3 (9.88)
Median	4.7
Min , Max	-22.0 , 24.7
3MSCT (stairs/min): Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	[redacted] ([redacted])
Median	[redacted]
Min , Max	[redacted] ([redacted])
Urine KS (ug/g): % Change from Baseline to Week 24 (MOR-005 Week 0)	
n	54
Mean (SD)	-45.1 (19.89)
Median	-50.8
Min , Max	-79.4, 5.3
Urine KS (ug/g): % Change from Baseline to Week 36 (MOR-005 Week 12)	
n	52
Mean (SD)	-48.0 (17.49)
Median	-52.7
Min , Max	-78.5 , 4.2
Urine KS (ug/g): % Change from Baseline to Week 48 (MOR-005 Week 24)	
n	52
Mean (SD)	-49.5 (16.70)
Median	-53.9
Min , Max	-72.9 , -0.3
Urine KS (ug/g): % Change from Baseline to Week 72 (MOR-005 Week 48)	
n	51
Mean (SD)	-53.7 (17.45)
Median	-56.6
Min , Max	-94.8 , -18.0
Urine KS (ug/g): Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	[redacted] ([redacted])
Median	[redacted]
Min , Max	[redacted] ([redacted])
FVC (L): % Change from Baseline to Week 24 (MOR-005 Week 0)	
n	55
Mean (SD)	4.9 (11.98)
Median	3.3
Min , Max	-19.1, 53.5
FVC (L): % Change from Baseline to Week 48 (MOR-005 Week 24)	
n*	24
Mean (SD)	3.6 (13.09)
Median	5.2
Min , Max	-23.7, 22.8

FVC (L): % Change from Baseline to Week 72 (MOR-005 Week 48)	
n	53
Mean (SD)	8.4 (18.62)
Median	7.4
Min , Max	-22.8 , 102.3
FVC (L): Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	[redacted] ([redacted])
Median	[redacted]
Min , Max	[redacted] ([redacted])
FEV1 (L): % Change from Baseline to Week 24 (MOR-005 Week 0)	
n	53
Mean (SD)	58.8 (249.52)
Median	8.3
Min , Max	-90.0 , 1663.0
FEV1 (L): % Change from Baseline to Week 48 (MOR-005 Week 24)	
n*	23
Mean (SD)	53.9 (215.13)
Median	3.7
Min , Max	-93.3 , 994.0
FEV1 (L): % Change from Baseline to Week 72 (MOR-005 Week 48)	
n	50
Mean (SD)	30.4 (114.23)
Median	-5.1
Min , Max	-93.3, 529.0
FEV1 (L): Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	[redacted] ([redacted])
Median	[redacted]
Min , Max	[redacted] ([redacted])
MPS HAQ self care domain score: % Change from Baseline to Week 24 (MOR-005 Week 0)	
n	57
Mean (SD)	-0.3 (0.90)
Median	-0.1
Min , Max	-3.1 , 1.4
MPS HAQ self care domain score: % Change from Baseline to Week 48 (MOR-005 Week 24)	
n	54
Mean (SD)	-0.4 (1.38)
Median	-0.4
Min , Max	-4.4 , 3.2
MPS HAQ self care domain score: % Change from Baseline to Week 72 (MOR-005 Week 48)	
n	55
Mean (SD)	-0.5 (1.57)

Median	-0.5
Min , Max	-4.0 , 3.7
MPS HAQ self care domain score: Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	[redacted] ([redacted])
Median	[redacted]
Min , Max	[redacted] ([redacted])
MPS HAQ mobility domain score: % Change from Baseline to Week 24 (MOR-005 Week 0)	
n	57
Mean (SD)	-0.7 (1.59)
Median	-0.5
Min , Max	-7.2 , 2.6
MPS HAQ mobility domain score: % Change from Baseline to Week 48 (MOR-005 Week 24)	
n	54
Mean (SD)	-0.7 (1.71)
Median	-0.6
Min , Max	-6.0 , 4.4
MPS HAQ mobility domain score: % Change from Baseline to Week 72 (MOR-005 Week 48)	
n	55
Mean (SD)	0.7 (1.86)
Median	-0.5
Min , Max	-6.1 , 5.9
MPS HAQ mobility domain score: Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	[redacted] ([redacted])
Median	[redacted]
Min , Max	[redacted] ([redacted])
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 24 (MOR-005 Week 0)	
n	57
Mean (SD)	-2.3 (7.02)
Median	-2.0
Min , Max	-25.0 , 14.0
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 48 (MOR-005 Week 24)	
n	54
Mean (SD)	-1.7 (7.89)
Median	-1.0
Min , Max	-23.0 , 18.0
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 72 (MOR-005 Week 48)	
n	55
Mean (SD)	-1.8 (8.29)
Median	0.0

Min , Max	-23.0 , 20.0
MPS HAQ caregiver assistance domain score: Change from Baseline to Week 120 (MOR-005 Week 96)	
n	[redacted]
Mean (SD)	c
Median	[redacted]
Min , Max	[redacted] ([redacted])

*Week 48 assessment results included only subjects who reached Week 48 while in Part 1 of the study as there was no Week 48 assessment in Part 2. This led to a reduced sample size at Week 48.
**Two patients who completed MOR-004 did not subsequently enter MOR-005

Table 12: Wheelchair use data in MOR-005 ITT population for elosulfase alpha 2.0mg/kg QW

On study	MOR-004 baseline			
	Yes	No	NA	Total
Week 12				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
NA	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
NA	[redacted]	[redacted]	[redacted]	[redacted]
Week 48				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
NA	[redacted]	[redacted]	[redacted]	[redacted]
Week 72				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
NA	[redacted]	[redacted]	[redacted]	[redacted]
Week 96				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
NA	[redacted]	[redacted]	[redacted]	[redacted]
Week 120				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
NA	[redacted]	[redacted]	[redacted]	[redacted]

A15. Please provide the change from baseline outcome data as specified in question A14 for the elosulfase alfa 2.0mg/kg qw arm of MOR-005 (and who also received this dose of elosulfase alfa in MOR-004; n=56) using the baseline from the start of MOR-004 (i.e. prior to start of treatment with elosulfase) for:

a) the per protocol population;
b) the MPP population.

Change in baseline data for most of the outcomes specified above (6MWT, 3MSCT, urine KS) for the PP and MPP populations have been provided in the tables below. These analyses were specified a priori and included in the SAP.

As no patient died during the MOR-004 and MOR-005 trials, analyses on change in baseline for mortality have not been conducted (BioMarin, 2013, BioMarin, 2017).

As explained in question A8, the PP population was previously used to perform sensitivity analyses for the efficacy endpoints in Part I but given that the final CSR is based on follow-up of 120 weeks or more for most subjects, the amount of data omitted in a PP analysis would be largely using the same criteria. At a study Steering Committee Investigator meeting on February 8, 2015 where analyses of Week 120 data were presented, it was agreed that the PP analyses population was too restrictive, limiting the data to less than 50% of subjects at Week 120. For this reason, analyses at week 120 for the PP population were not conducted and a modified per protocol (MPP) population was defined for this longer-term study, replacing the PP population in the CSR shared with the committee. Therefore, data for the PP population at 120 weeks is not available. In addition, to adequately respond to this question, BioMarin conducted post-hoc analyses on the MPP population for change in baseline data for FVC, FEV1, MPS HAQ and wheelchair use, and these have been added in the tables below. However, due to the fact that the PP population is no longer used in the CSR and has been replaced by the MPP population, these analyses were not conducted for the PP population.

Table 13: Change from baseline outcome data in MOR-005 PP and MPP populations

Outcome	Elosulfase alpha 2.0mg/kg QW (n=43)	Elosulfase alpha 2.0mg/kg QW (n=52)
	MPP population	**PP population**
6MWT (meters): Change from Baseline to Week 24 (MOR-005 Week 0)		
n	43	52
Mean (SD)	41.5 (59.89)	39.4 (57.63)
Median	22.8	25.0
Min , Max	-41.4 , 228.7	-57.8 , 228.7
6MWT (meters): Change from Baseline to Week 36 (MOR-005 Week 12)		
n	42	47
Mean (SD)	44.4 (53.94)	41.6 (55.36)
Median	40.8	38.1
Min , Max	-37.5 , 228.9	-61.5 , 228.9
6MWT (meters): Change from Baseline to Week 48 (MOR-005 Week 24)		
n*	19	22
Mean (SD)	37.4 (73.05)	45.3 (58.94)
Median	26.5	43.1
Min , Max	-120.0 , 181.5	-33.8 , 181.5
6MWT (meters): Change from Baseline to Week 72 (MOR-005 Week 48)		
n	43	35
Mean (SD)	37.5 (72.17)	43.5 (73.63)
Median	32.0	40.4
Min , Max	-120.0 , 229.3	-137.4 , 229.3
6MWT (meters): Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]
Min , Max	[redacted] ([redacted])	[redacted] ([redacted])
3MSCT (stairs/min): Change from Baseline to Week 24 (MOR-005 Week 0)		
n	43	52
Mean (SD)	3.9 (7.67)	4.7 (8.02)
Median	4.3	3.9
Min , Max	-12.4 , 17.8	-12.4 , 20.5
3MSCT (stairs/min): Change from Baseline to Week 36 (MOR-005 Week 12)		
n	42	48
Mean (SD)	5.7 (8.69)	6.0 (8.49)
Median	4.1	4.6
Min , Max	-16.2 , 27.2	-16.2 , 27.2
3MSCT (stairs/min): Change from Baseline to Week 48 (MOR-005 Week 24)		
n*	19	23
Mean (SD)	7.4 (11.35)	8.8 (9.47)
Median	4.8	4.8
Min , Max	-22.0 , 26.7	-2.3 , 30.4

3MSCT (stairs/min): Change from Baseline to Week 72 (MOR-005 Week 48)		
n	43	35
Mean (SD)	5.7 (9.98)	6.5 (9.09)
Median	5.3	6.0
Min , Max	-22.0 , 24.7	-20.7 , 21.2
3MSCT (stairs/min): Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]
Min , Max	[redacted] ([redacted])	[redacted] ([redacted])
Urine KS (ug/g): % Change from Baseline to Week 24 (MOR-005 Week 0)		
n	40	49
Mean (SD)	44.9 (19.60)	-44.9 (20.45)
Median	-50.8	-51.0
Min , Max	-79.4 , 5.3	-79.4 , 5.3
Urine KS (ug/g): % Change from Baseline to Week 36 (MOR-005 Week 12)		
n	42	43
Mean (SD)	-47.2 (18.73)	-47.2 (17.46)
Median	-51.1	-52.3
Min , Max	-78.5 , 4.2	-78.5 , 4.2
Urine KS (ug/g): % Change from Baseline to Week 48 (MOR-005 Week 24)		
n	41	46
Mean (SD)	-48.5 (17.28)	-50.0 (15.81)
Median	-51.8	-55.1
Min , Max	-71.8 , -0.3	-72.9 , -5.6
Urine KS (ug/g): % Change from Baseline to Week 72 (MOR-005 Week 48)		
n	41	31
Mean (SD)	-53.7 (17.87)	-54.2 (18.00)
Median	-56.6	-59.1
Min , Max	-94.8 , -18.0	-94.8 , -18.0
Urine KS (ug/g): Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]
Min , Max	[redacted] ([redacted])	[redacted] ([redacted])
FVC (L): % Change from Baseline to Week 24 (MOR-005 Week 0)		
n	40	NA
Mean (SD)	0.0 (0.09)	NA
Median	0.0	NA
Min , Max	-0.2, 0.3	NA
FVC (L): % Change from Baseline to Week 48 (MOR-005 Week 24)		
n*	17	NA
Mean (SD)	0.0 (0.16)	NA

Median	0.0	NA
Min , Max	-0.4, 0.3	NA
FVC (L): % Change from Baseline to Week 72 (MOR-005 Week 48)		
n	41	NA
Mean (SD)	0.1 (0.14)	NA
Median	0.1	NA
Min , Max	-0.3, 0.4	NA
FVC (L): Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]
FEV1 (L): % Change from Baseline to Week 24 (MOR-005 Week 0)		
n	40	NA
Mean (SD)	0.0 (0.08)	NA
Median	0.0	NA
Min , Max	-0.2, 0.2	NA
FEV1 (L): % Change from Baseline to Week 48 (MOR-005 Week 24)		
n*	17	NA
Mean (SD)	0.0 (0.15)	NA
Median	0.1	NA
Min , Max	-0.4, 0.3	NA
FEV1 (L): % Change from Baseline to Week 72 (MOR-005 Week 48)		
n	41	NA
Mean (SD)	0.0 (0.11)	NA
Median	0.0	NA
Min , Max	-0.2, 0.4	NA
FEV1 (L): Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]
MPS HAQ self care domain score: % Change from Baseline to Week 24 (MOR-005 Week 0)		
n	43	NA
Mean (SD)	0.4 (0.95)	NA
Median	-0.2	NA
Min , Max	-3.1, 1.4	NA
MPS HAQ self care domain score: % Change from Baseline to Week 48 (MOR-005 Week 24)		
n	43	NA
Mean (SD)	-0.6 (1.38)	NA
Median	-0.4	NA
Min , Max	-4.4, 3.2	NA
MPS HAQ self care domain score: % Change from Baseline to Week 72 (MOR-005 Week 48)		

n	43	NA
Mean (SD)	-0.7 (1.41)	NA
Median	-0.5	NA
Min , Max	-4.0, 3.7	NA
MPS HAQ self care domain score: Change from Baseline to Week 96 (MOR-005 Week 72)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]
MPS HAQ self care domain score: Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]
MPS HAQ mobility domain score: % Change from Baseline to Week 24 (MOR-005 Week 0)		
n	43	NA
Mean (SD)	-0.9 (1.66)	NA
Median	-0.7	NA
Min , Max	-7.2, 2.6	NA
MPS HAQ mobility domain score: % Change from Baseline to Week 48 (MOR-005 Week 24)		
n	43	NA
Mean (SD)	-0.7 (1.83)	NA
Median	-0.6	NA
Min , Max	-6.0, 4.4	NA
MPS HAQ mobility domain score: % Change from Baseline to Week 72 (MOR-005 Week 48)		
n	43	NA
Mean (SD)	-0.8 (1.73)	NA
Median	-0.5	NA
Min , Max	-6.1, 2.1	NA
MPS HAQ mobility domain score: Change from Baseline to Week 96 (MOR-005 Week 72)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]
MPS HAQ mobility domain score: Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 24 (MOR-005 Week 0)		
n	43	NA
Mean (SD)	NA	NA

Median	-2.0	NA
Min , Max	-25.0, 14.0	NA
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 48 (MOR-005 Week 24)		
n	43	NA
Mean (SD)	-1.9 (7.77)	NA
Median	-1.0	NA
Min , Max	-23.0, 18.0	NA
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 72 (MOR-005 Week 48)		
n	43	NA
Mean (SD)	-2.6 (8.07)	NA
Median	0.0	NA
Min , Max	-23.0, 20.0	NA
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 96 (MOR-005 Week 72)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]
MPS HAQ caregiver assistance domain score: % Change from Baseline to Week 120 (MOR-005 Week 96)		
n	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted]
Median	[redacted]	[redacted]
Min , Max	[redacted], [redacted]	[redacted]

*Week 48 assessment results included only subjects who reached Week 48 while in Part 1 of the study as there was no Week 48 assessment in Part 2. This led to a reduced sample size at Week 48.
SOURCE: (BioMarin, 2017)

Table 14: Summary of wheelchair use in MOR-005 MPP population (BioMarin data on file, 2021)

Study Visit	**Wheelchair Use**	**Elosulfase alpha 2.0mg/kg QW (n=[redacted])**
Baseline	No Use	[redacted] ([redacted]%)
	Some Use	[redacted] ([redacted]%)
	Always Use	[redacted] ([redacted]%)
	Yes - not specified	[redacted] ([redacted]%)
Week 12	No Use	[redacted] ([redacted]%)
	Some Use	[redacted] ([redacted]%)
	Always Use	[redacted] ([redacted]%)
	Yes - not specified	[redacted] ([redacted]%)
Week 24 (MOR-005 Week 0)	No Use	[redacted] ([redacted]%)
	Some Use	[redacted] ([redacted]%)
	Always Use	[redacted] ([redacted]%)
	Yes - not specified	[redacted] ([redacted]%)
Week 48 (MOR-005 Week 24)	No Use	[redacted] ([redacted]%)
	Some Use	[redacted] ([redacted]%)
	Always Use	[redacted] ([redacted]%)
Week 72 (MOR-005 Week 48)	No Use	[redacted] ([redacted]%)
	Some Use	[redacted] ([redacted]%)
	Always Use	[redacted] ([redacted]%)
Week 96 (MOR-005 Week 72)	No Use	[redacted] ([redacted]%)
	Some Use	[redacted] ([redacted]%)
	Always Use	[redacted] ([redacted]%)
Week 120 (MOR-005 Week 96)	No Use	[redacted] ([redacted]%)
	Some Use	[redacted] ([redacted]%)
	Always Use	[redacted] ([redacted]%)

A16. Please provide the results of change from baseline in endurance for the MAA study arms data presented in Figure 18 of the CS by age subgroup <18years and >=18years.

Endurance (6MWT) was stable or numerically improved regardless of age at treatment initiation, particularly when compared to natural history data from the MOR-001 study (see below Figure).

- In the age group of patients who were < 18 years old at baseline (n=[redacted], mean treatment duration [redacted] years), the percent change from baseline to the last follow-up was [redacted]% (+[redacted] m) for 6MWT;

- In the age group of patients who were ≥ 18 years old at baseline (n=[redacted], mean treatment duration [redacted] years), the percent change from baseline to the last follow-up was [redacted]% (+[redacted] m) for 6MWT;

- Overall, in MOR-001 in 2 years of follow-up, the annual change in 6MWT distance was -6.84 m.

Figure 1: Six-minute walk test (6MWT) distance over time by age subgroup vs. untreated patients in the MOR-001 study (BioMarin MAA data on file, 2021)

Figure 2: Box plot of 6MWT change from baseline by age subgroup (BioMarin MAA data on file, 2021)

Discontinuations and study treatment

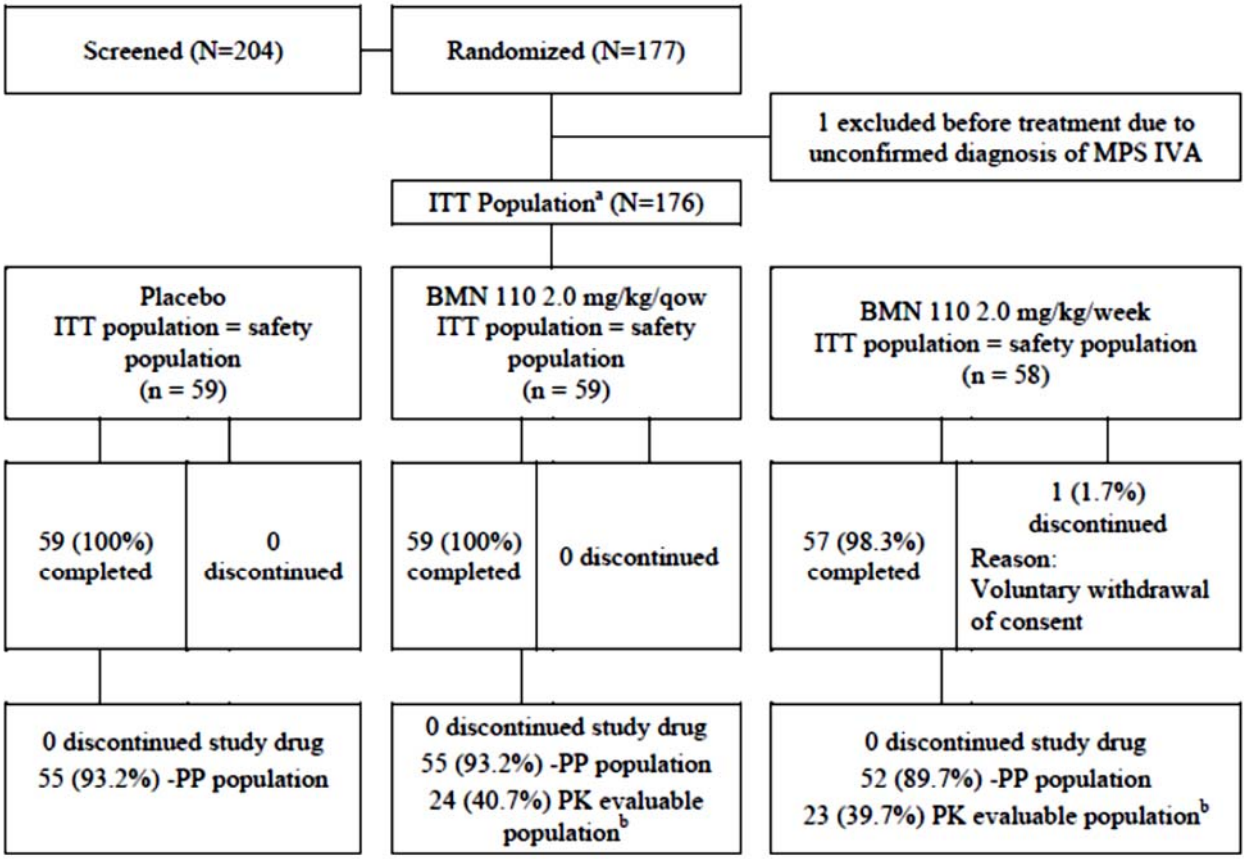
A17. Please provide a CONSORT flow diagram including numbers and reasons for all discontinuations for the following populations and trials by treatment arm:

a) MOR-004;
b) MOR-005 ITT population;
c) MOR-005 MPP population;
d) MOR-005 PP population.

CONSORT flow charts are presented here for the participants in the two RCTs: MOR-004 and MOR-005.

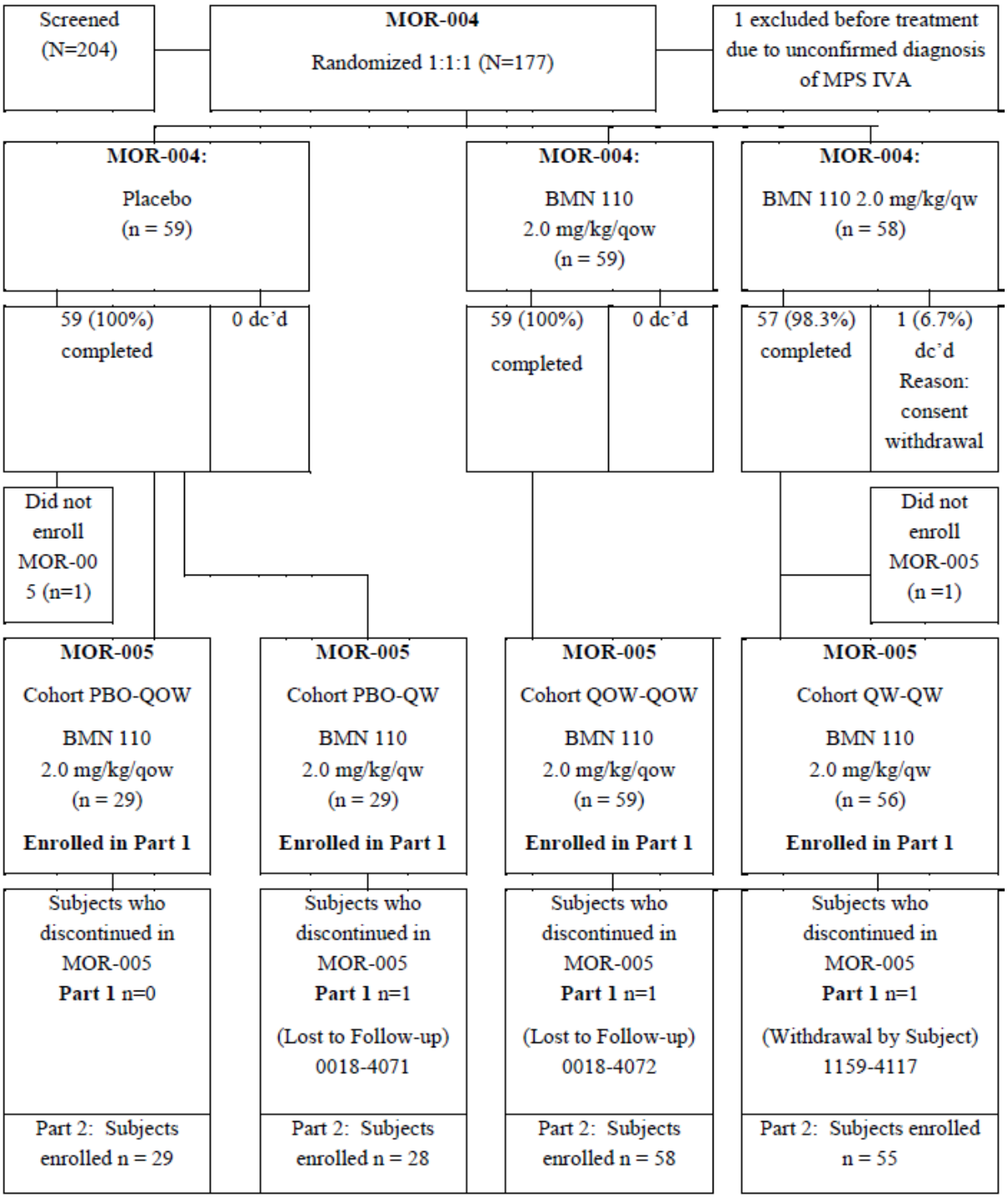
The disposition of participants in the MOR-004 study is shown in the figure below.

Figure 3: Disposition of participants in MOR-004 (BioMarin, 2013)



The disposition of participants in the MOR-005 study is shown in the figure below.

Figure 4: Disposition of participants in MOR-005 (ITT and PP populations) (BioMarin, 2017)



Subjects who discontinued in MOR-005 **Part 2**		Subjects who discontinued in MOR-005 **Part 2**		Subjects who discontinued in MOR-005 **Part 2**		Subjects who discontinued in MOR-005 **Part 2**
n = 29		n = 28		n = 58		n = 55
n = 28 due to Study Termination by Sponsor n = 1 due to Withdrawal by Subject		n = 28 due to Study Termination by Sponsor		n = 49 due to Study Termination by Sponsor n = 4 due to Withdrawal by Subject n = 3 due to AE n = 1 due to lost to Follow-up n = 1 "other"		n = 53 due to Study Termination by Sponsor n = 2 due to AE

MOR-005 MPP population excluded patients who underwent orthopaedic surgery during the study (n=38) and/or exhibited recurrent noncompliance with the study protocol. Missed infusions were used as an indicator of compliance; patients missing ≥20% of their scheduled elosulfase alfa infusions during MOR-005 were identified as noncompliant (n=14). In total, 49 patients were excluded, thereby allowing inclusion of an additional 46 patients as compared to the PP population (BioMarin, 2017).

A18. Please provide details of the number of patients who discontinued each study and the reason for discontinuations in the following studies:

a) MOR-001 full study population;
b) patients in MOR-001 after matching to MOR-005;
c) MAA ex-trial patients;
d) MAA treatment naive patients.

a) <u>MOR-001 (MorCAP):</u>

Originally, MorCAP (MOR-001) was a single visit, cross sectional study of MPS IVA patients without limitations on age or symptom severity with the first patient enrolling in 2008. In order to gain more detailed insight into the natural history of MPS IVA, the study was then amended to be longitudinal and in 2011 and included a total of 353 subjects (Harmatz et al., 2013). In total, 123 out of 353 subjects discontinued in order to enrol in ERT clinical trials (Harmatz et al., 2015).

b) Patients in MOR-001 after matching to MOR-005:

123 patients overall in MOR-001 discontinued the study to enrol in ERT clinical trials. It is not reported, however, how many of this subgroup of patients matched to Phase-3 MOR-005 (n=97) did enrol in MOR-005 and discontinued during the study.

c) MAA ex-trial patients:
[redacted].

d) MAA treatment-naïve patients: In the treatment-naïve group:
[redacted]

A19. Please provide the proportion of people who have missed one or more infusions (including mean and SD) in the following studies along with the reasons for missed infusions:

a) each trial arm in MOR 004;
b) each trial arm in MOR-005;
c) the ex-trial arm in the MAA study; and
d) the treatment naive arm in the MAA study.

a) MOR-004 missed infusions

Please refer to Table 10.3.1 below (or in the CSR page 140) and source Table 14.1.13 (pages 586-588) and Table 14.1.14 (pages 589-590) (BioMarin, 2013).

All study drug infusions were administered at a clinical site. Treatment compliance was measured with respect to proportion of missed or incomplete infusions, number of subjects with missed infusions, and total actual dose (mg/kg) as a percentage of the total planned dose.

The number of missed infusions (and proportion of missed to planned infusions) was low overall but higher in the BMN 110 treatment groups compared with placebo:

- [redacted] in the placebo group
- [redacted] in the BMN 110 2.0 mg/kg/qow group, and
- [redacted] in the BMN 110 2.0 mg/kg/week group

A similar imbalance is noted in the number of subjects with missed infusions (see Table 14.1.14 in the CSR page 589).

Although there is a difference between groups, the reasons for missed infusions varied widely for individual subjects, and no cause-specific or site-specific reasons were identified. Reasons that a subject did not receive study drug infusion included, among others:

- Concurrent illness:
    - [redacted] in placebo arm
    - [redacted] in BMN 110 2.0 mg/kg/qow arm; and
    - [redacted] subjects in BMN 110 2.0 mg/kg/week arm
- AE:
    - [redacted] subject in placebo arm
    - [redacted] in BMN 110 2.0 mg/kg/qow
    - [redacted] in BMN 110 2.0 mg/kg/week)
- For inability to cannulate a vessel:
    - [redacted] in placebo arm
    - [redacted] in BMN 110 2.0 mg/kg/qow
    - [redacted] in BMN 110 2.0 mg/kg/week
- Or for personal reasons, such as transportation difficulties:
    - [redacted] in placebo
    - [redacted] in BMN 110 2.0 mg/kg/qow
    - [redacted] BMN 110 2.0 mg/kg/week

Table 15: Study Drug Treatment Compliance in MOR-004 ITT Population (MOR-004 CSR: Table 10.3.1)

[redacted]

b) MOR-005 missed infusions (BioMarin, 2017):

Please refer to Table 11.3.1 below or pages 120-121 in CSR MOR-005. Study drug treatment compliance is provided in Table 14.1.16.4 (page 607 in CSR), Study drug infusion schedule compliance is provided in Table 14.1.14.4 (page 603 in CSR).

All study drug infusions were administered at a clinical site. Treatment compliance was measured with respect to the proportion of missed or incomplete infusions, number of

subjects with missed infusions, and total actual dose (mg/kg) as a percentage of the total planned dose.

Subjects in each treatment group received a similar mean number of infusions, had a similar mean number of incomplete infusions, and achieved similar and high mean dosing compliance (range [redacted]% to [redacted]%). The mean dosing compliance was the Total population was [redacted]% (see Table below). In the following cohorts, the percentage of infusions outside the 3-day dosing window (Table 14.1.14.4) were:

- Placebo-QOW, [redacted]%
- PBO-QW, [redacted]%
- QOW-QOW, [redacted]%
- QW-QW, [redacted]%
- Total population, [redacted]%

The proportion of missed to planned infusions was low overall (total population, [redacted]%), but slightly higher in cohort PBO-QW ([redacted]%) compared with cohort PBO-QOW ([redacted]%), QW-QW ([redacted]%), and QOW-QOW ([redacted]%) (see Table below). Reasons for discontinuation were not reported in the MOR-005 CSR.

Table 16: Study Drug Treatment Compliance in MOR-004 and MOR-005 ITT population (MOR-005 CSR Table 11.3.1)

[redacted]

c) MAA ex-trial patients missed infusions:

Table 17: Treatment compliance in MAA ex-trial patients

MAA (Ex-Trial)	Year 1 (n=[redacted])	Year 2 (n=[redacted])	Year 3 (n=[redacted])
Number of yearly infusions per patient	[redacted]	[redacted]	[redacted]
Number of Patients Missing one or more infusion	[redacted]	[redacted]	[redacted]
Total infusions	[redacted]	[redacted]	[redacted]
Total Missed Infusions	[redacted]	[redacted]	[redacted]
Total Missed Infusions (SD)	[redacted]	[redacted]	[redacted]
Missed Infusions as % of total scheduled infusion	[redacted]	[redacted]	[redacted]

MAA treatment-naïve patients missed infusions:

Table 18: MAA treatment compliance in ERT-naïve patients

MAA (ERT-Naïve)	Year 1 (n=[redacted])	Year 2 (n=[redacted])	Year 3 (n=[redacted])
Number of yearly infusions per patient	[redacted]	[redacted]	[redacted]
Number of Patients Missing one or more infusion	[redacted]	[redacted]	[redacted]
Total infusions	[redacted]	[redacted]	[redacted]
Total Missed Infusions	[redacted]	[redacted]	[redacted]

Total Missed Infusions (SD)	[redacted]	[redacted]	[redacted]
Missed Infusions as % of total scheduled infusion	[redacted]	[redacted]	[redacted]

MAA – All patients:

Table 19: Treatment compliance in all MAA patients

MAA (All patients)	Year 1	Year 2	Year 3
Total Missed Infusions	[redacted]	[redacted]	[redacted]
Total Missed Infusions with reasons reported	[redacted]	[redacted]	[redacted]
Medically Approved missed infusions (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Reported reasons			
Holiday (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Pyrexial (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
IV access issues (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
unwell (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
fridge issues (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
illness (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
In hospital (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Nurse unable to cannulate (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Pain; had treatment break due to port issues (% of total missed infusions)	[redacted] ([redacted]%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)

A20. Please provide the proportion of people who have missed 20% or more of their scheduled elosulfase alfa infusions (including mean and SD) in the following studies along with the reasons for missed infusions:

a) each trial arm in MOR 004;
b) each trial arm in MOR-005;
c) the ex-trial arm in the MAA study; and
d) the treatment naive arm in the MAA study.

a) MOR-004 (BioMarin, 2013):

No subjects have missed 20% or more of their scheduled elosulfase alfa infusions in MOR-004. Please refer to question A19 above.

b) MOR-005 (BioMarin, 2017):

No subjects have missed 20% or more of their scheduled elosulfase alfa infusions in MOR-005. Please refer to question A19 above.

+ d) MAA patients (ex-trial and treatment-naïve patients)

[redacted]

A rank of patients with more than 1 missed infusion is provided in the table below:

Ex-trial patients:

Table 20: Missed infusions and reasons for missed infusions in MAA ex-trial patients

Study	Timepoint	Missed Infusions	Medically Approved (n)	Reasons (n)
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]

Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]
Ex-Trial	[redacted]	[redacted]	[redacted]	[redacted]

<u>Treatment-naïve patients</u>:

Table 21: Missed infusions and reasons for missed infusions in MAA ERT-naïve patients

Study	Timepoint	Missed Infusions	Medically Approved (n)	Reasons (n)
Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]

Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Tx-naïve	[redacted]	[redacted]	[redacted]	[redacted]

Other questions

A21. Please provide the CSRs or equivalent reports for:

a) MOR-004;
b) MAA; and
c) MOR-001 (MorCAP).

a) MOR-004: The CSR for MOR-004 is hereby enclosed as requested for the ERG's review.
b) MAA: There is no CSR for the Managed Access Agreement in England, as this is not study.
c) MOR-001 (MorCAP): There is no CSR for MOR-001. The following publications – Harmatz et al. 2013 and Harmatz et al. 2015 – provide data on these patients and are available on NICE Docs.

A22. Please provide the paper referred to as Harmatz et al., 2013a AB in Table 47 (Mortality) of the CS and provide a summary of the study and the rationale for its inclusion in Table 47.

The abstract from Harmatz et al., 2013a has been copied below and uploaded on NICE Docs. It was included in Table 47 (Mortality), as part of the systematic review on safety conducted in December 2019, which also included abstracts (Harmatz, 2013).

Long term safety analysis of BMN110 dosed at 2 mg/kg/week in 52 subjects with mucopolysaccharidosis (Morquio A syndrome, MPSIVA)

Abstract
A clinical development program investigating safety and efficacy of BMN110, an enzyme replacement therapy for treatment of MPSIVA, was conducted. A long-term safety analysis was done on a subset of 52 subjects with >48 weeks (49-100.1 weeks) of BMN110 exposure at 2.0 mg/kg/week. Mean duration of exposure was 75.3(± 17.49) weeks, and mean weekly dose was 1.99 (± 0.039) mg/kg. To account for varying durations of follow-up in ongoing studies, frequencies of adverse events (AEs) are reported as standardized on an annualized basis. Mean subject year frequency of all AEs decreased from 33.33 during the 1-12-week interval to 11.68 during the >48-week treatment duration. Subject-year frequency of the most common AEs, including vomiting, pyrexia, and headache, decreased with treatment duration. Infusion Associated Reactions (IARs) were reported for all subjects, and mean subject-year frequencies decreased with treatment duration. Overall, mean annualized frequency was 11.13 IARs per subject-year. The most common IARs by incidence (and annualized frequency) were pyrexia, 51.9% (0.91), vomiting 46.2% (1.13), and headache 38.5% (1.04). Of the 3630 infusions administered, 23 (0.63%) were interrupted/discontinued due to an AE requiring medical intervention. **There were no deaths and no AEs resulting in permanent study discontinuation reported in this subset of subjects**.

http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71346054
http://dx.doi.org/10.1007/s10545-013-9633-z

P. Harmatz, Children's Hospital and Research Center, Oakland, United States

A23. Please provide the numbers of people in addition to the percentages already provided in Table 54 (Change in wheelchair use after 120 weeks of treatment with 2.0 mg/kg/QW of elosulfase alfa compared to MOR-001) of the CS.

Table 22: Change in wheelchair use after 120 weeks of treatment with 2.0 mg/kg/QW of elosulfase alfa compared to MOR-001 (Table 54 in CS):

	Wheelchair health state at Baseline		
Wheelchair health state at week 120 (MOR-005)	**No WC**	**Occ. WC**	**Always WC**
No WC	[redacted]	[redacted]	[redacted]
Occ. WC	[redacted]	[redacted]	[redacted]
Always WC	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

	Wheelchair health state at Baseline		
Wheelchair health state at 2 years (MOR-001)	**No WC**	**Occ. WC**	**Always WC**
No WC	[redacted]	[redacted]	[redacted]

Occ. WC	[redacted]	[redacted]	[redacted]
Always WC	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

A24. Please clarify whether the baseline characteristics for the ex-trial MAA patients presented in Table 25 of the CS relate to the baseline at the start of the MAA or the baseline from the original trials.

The baseline characteristics for ex-trial MAA patients that are presented in Table 25 of the CS relate to the baseline characteristics from the original trials, i.e., pre-treatment with elosulfase alfa.

A25. Please clarify whether the treatment duration for the MAA patients provided in Table 25 relates to the start or end of the MAA. If it relates to the start, please explain the treatment duration of [redacted] years for the treatment naive patients. Please also clarify what the min and max values presented below the median treatment duration relate to as the max is lower than the median.

The treatment duration provided in Table 25 is calculated based on treatment start date and the last assessment available in the Data Cut of [redacted]. For the Ex-Trial patients, the treatment start date relates to treatment start in the clinical trial setting. For the ERT-Naïve Patients, the treatment start date relates to treatment start in the MAA.

The median reported for the treatment duration in Table 25 was incorrectly rounded to [redacted]. Please find below the corrected figures:

Table 23: MAA treatment duration in ex-trial and ERT-naïve patients

	Ex-Trial (Patients initiation treatment before MAA)	**ERT-Naïve Patients (Patients initiating treatment in MAA)**
Treatment Duration, years		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]

Min, Max	[redacted], [redacted]	[redacted], [redacted]

There is an additional clarification related to Table 25: “Age at enrolment” should read “Age at baseline”.

A26. Please clarify the mean treatment duration for the MAA ex-trial patients (n=[redacted]) detailed on page 175 as [redacted] years but in Table 25 (MAA baseline characteristics) it is reported as [redacted] years. Please also provide the mean (with SD) treatment duration (and the median and range) for ex-trial patients at baseline in the MAA and at the latest data collection point in the MAA (to correspond with the MAA outcome data presented in the CS).

The treatment duration in the MAA varies due to the availability of assessments per outcomes. The treatment duration provided in Table 25 is based on the treatment start and the last data point available in the data cut [redacted].

The treatment duration reported for each of the outcomes is calculated based on the latest data point available for each patient, whilst in Table 25 the treatment duration is calculated in the last data point available across all outcomes.

As request, in the Table below is reported the treatment duration of Ex-Trial at MAA enrolment and the treatment duration as the data cut (Table 25).

Table 24: MAA treatment duration in ex-trial patients at MAA enrolment and at last follow-up

	Ex-Trial (Patients initiation treatment before MAA)	
	Treatment Duration at last data point available in the data cut, years	Treatment Duration at MAA enrolment, years
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]

A27. Please provide details of mortality for patients in the MAA and if there were any deaths please specify which treatment group they occurred in?

There were no deaths until the data cut-off of [redacted]. One patient deceased after the data cut, but we are not aware of the reason or the treatment group of this patient.

Section B: Clarification on cost-effectiveness data

All scenario analyses should be provided as flexible options in the model (i.e. in the form of a drop-down menu or a check box) so that these can be incorporated simultaneously in the same ICER as needed. Deterministic and probabilistic results should be provided in case the company changes its base case ICER. Further clarification requested on 08/02/21: Please can the company clarify if their base case ICER has changed (the new model submitted shows an ICER of £[redacted]. Also, please can the company confirm if this is their updated base case ICER and, if so, please provide probabilistic results based on the new ICER.

Company's response submitted on 12/02/21:

The base case ICER hasn't changed from the original submission. The table below. However, all the new assumptions, as suggested by ERG has been incorporated as a drop-down menu in the "Scenario Management" sheet.

Discounted results	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

In question B1, B4 and B5 the ERG asked that the company use annual data for the respective cycles in the model from MorCAP and from the MAA dataset. The company's replies do not address the ERG's request in any of these questions. To aid with the interpretation of the ERG's requests, we have produced the tables below. When rereferring to the use of annual data in the model, the ERG means to populate the tables below with the respective data, and then use these tables for the transition probabilities in the company's model as a scenario analysis (or as a new base case analysis, depending on the company's decision).

Transition probabilities in the comparator arm to be used in year 1 of the model (does not need altering from company's analysis):

BioMarin's updated response submitted on 22/02/2021: Updated responses to B1, B4 and B5 provided below.

Annual transition probabilities for the comparator arm (from MOR-001) from baseline to Y1 and Y1 to Y2 are provided in the table below.

MOR-001 (baseline to Y1)		From			
		No wheelchair use	Some wheelchair use	Wheelchair dependent	Total n
To	No wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities in the comparator arm to be used in year 2 of the model:

MOR-001 (data from year 1 to year 2)		From			
		No wheelchair use	Some wheelchair use	Wheelchair dependent	Total n
To	No wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities in the comparator arm to be used in year 3+ of the model: Please make any necessary assumptions (and explicitly document them) from year 3 onwards (please note the considerations made in question B2 to extrapolate data).

Transition probabilities in the ESA arm:

When based on the ERT-naïve data (as per company's base case – see question B5):

Transition probabilities in the ESA arm to be used in year 1 of the model:

BioMarin's updated response submitted on 22/02/2021: There are total of [redacted] patients in the MAA database as on November 2019. Of these [redacted], [redacted] were ex-trial patients, and [redacted] treatment naïve patients. Baseline characteristics of these patients are presented in the table below:

	Ex-Trial (Patients initiation treatment before MAA)	**ERT-Naïve Patients (Patients initiating treatment in MAA)**
N	[redacted]	[redacted]
Female, number (%)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Age at enrolment, years		
N	[redacted]	[redacted]
Mean (SD)	[redacted] ([redacted]%)	[redacted] ([redacted]%)
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
Treatment Duration, years		
N	[redacted]	[redacted]
Mean (SD)	[redacted], [redacted]	[redacted], [redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
Weight, kg		
N	[redacted]	[redacted]
Mean (SD)	[redacted], [redacted]	[redacted], [redacted]
Median	[redacted]	[redacted]

Min, Max	[redacted], [redacted]	[redacted], [redacted]
6MWT, meters		
N	[redacted]	[redacted]
Mean (SD)	[redacted], [redacted]	[redacted], [redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
FVC, L		
N	[redacted]	[redacted]
Mean (SD)	[redacted], [redacted]	[redacted], [redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
FEV1, L		
N	[redacted]	[redacted]
Mean (SD)	[redacted], [redacted]	[redacted], [redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
Ejection fraction, %		
N	[redacted]	[redacted]
Mean (SD)	[redacted], [redacted]	[redacted], [redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted], [redacted]	[redacted], [redacted]
uKS, µg/mg creatinine		

N	[redacted]	[redacted]
Mean (SD)	[redacted], [redacted]	[redacted], [redacted]
Median	[redacted]	[redacted]

The wheelchair use at baseline was available for [redacted] patients (of the total of [redacted] patients who were treatment naïve). The mean treatment duration was [redacted] years for treatment naïve patients.

For calculating transition probabilities following assumptions have been made:

1. MPS-HAQ
    a. Q33, if response is no (0) to this question – no WC use
    b. Q33a, if response is the first 3 options (1,2,3) – some WC use
    c. Q33a, if response is 4th option (always) – always WC use
2. For [redacted] patient there was WC use status at baseline, Y1 and 18 months. 18 months value was used as transition from Y1 to Y2.

ERT-naive patients Year 0 to year 1		**From**			
		No wheelchair use	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]	[redacted]	[redacted]	[redacted]
	Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
	Wheelchair dependant	[redacted]	[redacted]	[redacted]	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities in the ESA arm to be used in year 2 of the model:

ERT naive patients Year 1 to year 2		**From**			
		No wheelchair use	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]	[redacted]	[redacted]	[redacted]

	Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
	Wheelchair dependant	[redacted]	[redacted]	[redacted]	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities in the ESA arm to be used in year 3 of the model:

ERT naïve patients from year 2 to end of follow-up		**From**			
		No wheelchair use	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]	[redacted]	[redacted]	[redacted]
	Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
	Wheelchair dependant	[redacted]	[redacted]	[redacted]	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Based on these annual probabilities, a scenario analysis with new ICERs are presented below.

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

The QALY gain went down from [redacted] QALYs to [redacted] QALYs. The ICER was £[redacted].
The following assumptions have been made while populating the transition probabilities in the model:

- Transition probabilities for the comparator arm was available for baseline to Y1 and Y1 to Y2 (Please see the transition probability tables on page 62 of this document. Also, for the MAA treatment-naïve patients, transition probabilities were available up to Y3 (Please see the details on page 64-65).

- No changes were made to the transition probabilities beyond Y3. i.e. the probabilities remained same as in the original submission made on 11/12/2020.

Transition probabilities in the ESA arm to be used in year 4+ of the model:

Please make any necessary assumptions (and explicitly document them) from year 4 onwards (please note the considerations made in question B2 to extrapolate data).

When based on the ex-trial data (ERG's preference as indicated in question B1 and B4) and based on Figure 8 provided by the company:

BioMarin's updated response (22/02/21): Disposition of these [redacted] ex-trial patients are:

Trial Name	N
MOR-002	[redacted]
MOR-004	[redacted]
MOR-006	[redacted]
MOR-007	[redacted]
Total	[redacted]

All those [redacted] patients (ex-trial), [redacted] patients had baseline wheelchair (WC) status. I.e. WC status before the start of treatment. There were no follow-up WC status available from Y1 to Y4. Possibly, the WC status started getting measured through MPS-HAQ once patients entered into the MAA. The mean treatment duration was [redacted] years for ex-trial patients.

The assumptions for WC status remain the same as used for treatment naïve patients. i.e.

1. MPS-HAQ
    a. Q33, if response is no (0) to this question – no WC use
    b. Q33a, if response is the first 3 options (1,2,3) – some WC use
    c. Q33a, if response is 4th option (always) – always WC use

2. For [redacted] patient there was WC use status at baseline, Y1 and 18 months. 18 months value was used as transition from Y1 to Y2.

Of the [redacted] patients who had baseline WC status, [redacted] had WC status available at Y5 (first time WC status started appearing for the patients). For the missing yearly transitions from baseline to Y1, Y1 to Y2, Y2 to Y3, Y4 to Y4 and Y4 to Y5, following conversion of probability to rate was used.

Annual probability= 1-EXP(-(-ln(1-Risk)/number of cycles))

Thus, from the WC status available for [redacted] patients from baseline to Y5, the transition probabilities were:

Ex trial patients Year 0 to year 5		**From**			
		No wheelchair use	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]	[redacted]	[redacted]	[redacted]
	Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
	Wheelchair dependant	[redacted]	[redacted]	[redacted]	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

The 5-year transition probability was converted into annual probability using the formula 1-EXP(-(-ln(1-Risk)/number of cycles)), and hence transition probability from baseline to Y1, Y1 to Y2, Y2 to Y3, Y4 to Y4 and Y4 to Y5 is shown in the table below:

Ex trial patients baseline to Y1, Y1 to Y2, Y2 to Y3, Y4 to Y4 and Y4 to Y5		**From**			
		No wheelchair use	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]	[redacted]	[redacted]	[redacted]
	Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
	Wheelchair dependant	[redacted]	[redacted]	[redacted]	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Transition probability for the rest (from Y5 to Y6, Y6 to Y7) are shown in the tables below. It may be noted that there were total of [redacted] and [redacted] patients available for calculating transition probabilities from Y5 to Y6, and Y6 to Y7 respectively. For Y7 to Y8, there were [redacted] patients available in 'no WC use' state in the database to calculate transition probabilities. Same was the case for Y8 to Y9 and Y9 to Y10. Hence, last transition probability table is for Y6 to Y7.

Ex trial patients Y5 to Y6		**From**			
		No wheelchair use	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]	[redacted]	[redacted]	[redacted]
	Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
	Wheelchair dependant	[redacted]	[redacted]	[redacted]	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Ex trial patients Y6 to Y7		**From**			
		No wheelchair use	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]	[redacted]	[redacted]	[redacted]
	Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
	Wheelchair dependant	[redacted]	[redacted]	[redacted]	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Based on these annual probabilities, a scenario analysis with new ICERs are presented below.

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

The QALY gain went up from [redacted] QALYs to [redacted] QALYs. The ICER was £[redacted]. The following assumptions have been made while populating the transition probabilities in the model:

- Transition probabilities for the comparator arm was available for baseline to Y1 and Y1 to Y2 (Please see the transition probability tables on page 62 of this document. Also, for the MAA ex-trial patients, transition probabilities were available up to Y7 (Please see the details on page 66-69).
- For the comparator arm, transition probabilities from Y3 onwards was assumed to be same as in Y2 for the rest of the 5 cycles to Y7 (transition probabilities for the MAA ex-trial patients were available up to Y7).
- No changes were made to the transition probabilities beyond Y7. I.e. the probabilities remained same as in the original submission made on 11/12/2020.

Transition probabilities in the ESA arm to be used in year 11+ of the model:

Please make any necessary assumptions (and explicitly document them) from year 11 onwards (please note the considerations made in question B2 to extrapolate data).

Company's response submitted on 12/02/2021: As responded to in the email sent to NICE on 08/02/21 and 10/02/21, this requires structural changes to the model and company will provide its response by **22nd February, 2021.**

Model structure

B1. Priority question. In light of the following statements taken from the evaluation consultation document for the original HST for elosulfase:

"*The Committee [...] heard from the clinical and patient experts that the categories of wheelchair use in the clinical trials could have been subjective. They emphasised that patients use wheelchairs in different ways, to manage endurance and daily activities according to their individual needs, so the effect of treatment is not necessarily well represented by this measure. Furthermore, patients do not judge their quality of life by how*

much they are using the wheelchair. The Committee considered that this evidence was informative but was mindful of putting too much emphasis on it.";

"The Committee concluded that the key determinants of mortality are the respiratory and cardiac complications, and that what matters the most to people with the condition is the ability to carry out normal everyday activities with sufficient endurance and without pain or fatigue."

Please explain how/if the committee's concerns around the use of wheelchair-related outcomes in the economic analysis were addressed by the company in their new submission.

In the company submission, transition for the first 2 years are based on transition between wheelchair (WC) use health states in the MAA-ERT naive patients (shown in the figure below).

Figure 5: Patients showing stability, decline, or improvement in wheelchair status over time versus baseline (based on MPS-HAQ Mobility Q33 and Q33a regarding wheelchair use)

Figure 6: Proportion of patients treated with elosulfase alfa achieving long-term stability in Subsequent Years after the two initial cycles

	Asymptomatic	No wheelchair use	Some wheelchair use	Wheelchair dependent	End stage
Long-term stabiliser	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Mild decliner	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

The transitions beyond 2 years are based on responses to treatment with elosulfase alpha. The patients in 2+ years transitions have been categorised into '*Improved wheelchair status*', '*Stabilisation*' and '*Worsened wheelchair status*' based on the following definition. Please note that these 3 subsets were wrongly labelled as 'long-term stabiliser', 'mild decliner' and 'non-responders' in the company submission (cost-effectiveness model).

- *Improved wheelchair status:* these are patients who see a stabilization of disease due to continuous response to elosulfase alfa treatment. These patients would remain on treatment;
- *Stabilisation:* these are patients whom treatment with elosulfase alfa would lead to a reduced rate of disease progression compared to untreated patients. These patients would remain on treatment;

- *Worsened wheelchair status:* these are patients for whom elosulfase alfa would not change the rate of disease progression. These patients would discontinue treatment.

Clinical opinion indicated that the proportion of improved wheelchair and stabilisation status patients would vary according to WC health states and would depend on how much irreversible damage is already present when patients start treatment. The proportions of improved wheelchair and stabilisation status patients are detailed below:

- No WC use health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%
- Some WC use health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%
- WC dependent health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%
- Paraplegic health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%

Clinical opinion was that the rate of disease progression in stabilisation patients would be 30% of that of untreated patients (i.e. 6MWT would decline at 2.1m per annum instead of 7.1m).

To the committee's observation made in 2015 regarding the use of FVC to drive the model, the company did a linear regression model, based on all observations of patients enrolled in the MAA. The company also listened to clinical experts in England, who confirmed that FVC is not a reliable measure of endurance and functioning of the patients with MPS-IV, and sometimes may not be possible to measure in young children (especially due to challenges with spirometry). In the multiple linear regression analysis conducted by the company, it was found that pulmonary function (as measured by FVC) is not a significant predictor for wheelchair use. However, age and 6MWT were found to be significant predictors of wheelchair use. The linear regression is presented in the table below:

Figure 7: Linear regression analysis of FVC/FEV1, 6MWT, and age as predictors of wheelchair use

R-squared	[redacted]
p-value	[redacted]
Number of Observation	[redacted]

Wheelchair Use	Coeff.	Std. Err.	p-value	[95% Conf.Interval]	
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SIXMWT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Endurance (6MWT) and Age are significant predictors of wheelchair use. Therefore, the company reassures that the model's current structure in the base case is the most reasonable approach based on the evidence available.

Further, the Wheelchair Use is strongly associated with EQ5D. EQ-5D vs. wheelchair use (r = [redacted], n = [redacted], p<[redacted]), which means that patients who reported more use of Wheelchair have a lower utility score justifying the health states around the wheelchair Use. It may be noted that pulmonary function varies widely within and between patients and do not correlate well with MPS-HAQ mobility domain. Changes in entry and exit from the health states is currently driven by 6MWT.

[redacted]

This is further evidence in the original table 42 of the original submission (presented below).

Table 25: Pearson's correlations between clinical measures change from baseline

Variables	6MWT	FVC	FEV1	uKS	EQ-5D	MPS-HAQ (Mobility domain)	MPS-HAQ (Self-care domain)
6MWT	[redacted]						
FVC	[redacted]	[redacted]					
FEV1	[redacted]	[redacted]	[redacted]				

uKS	[redacted]	[redacted]	[redacted]	[redacted]			
EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
MPS-HAQ (Mobility domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MPS-HAQ (Self-care domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Values in bold are different from 0 with a significance level alpha = 0.05

As can be seen in the table above, [redacted]. The current model structure, which is driven by wheelchair status correlates strongly with EQ5D. Thereby justifying the sensitivity and reliability of wheelchair status as clinically meaningful health sate to be used in the model.

Owing to the reasons above changing the structure of the model to FVC (from current wheelchair use), may not be associated with health state rewards (EQ5D utility values), as evidenced by the regression results above.

B2. Priority question. In light of the views from the committee in the original HST, please consider changing the base case model structure (or providing a scenario analysis) so that the focus of the model is on FVC outcomes. Such a model should account for FVC progression from baseline in every health state (i.e. asymptomatic; no wheelchair use; sometimes wheelchair use; wheelchair dependent and paraplegic states). When developing the model please consider the following aspects:

In order to estimate the proportion of patients in the different wheelchair categories throughout the model (to estimate health state costs and other outcomes linked to wheelchair use in the model), please consider using the IPD data provided to the ERG on December 15th in sheet "Table 74- Ad-hoc analysis" (and/or an equivalent IPD dataset available from the MAA data named "MAA-dataset-Nov-19" to increase sample size) to estimate potential thresholds of FVC that might be associated with specific wheelchair states. For example, if the analysis of the IPD data shows that for the hypothetical FVC threshold of 5L to 1.5L, all patients are in the "no wheelchair

category", then as patients' FVC progresses through these specific thresholds, they can move across wheelchair categories.

Please estimate baseline FVC (L) for all wheelchair states (equivalent to those reported in Table 74 of the CS) using the outcomes of the matched analysis requested in question A2 (please justify any assumptions made to determine the values for the asymptomatic and paraplegic states);

Please estimate the decrease (or increase) in FVC (L) according to treatment arm for every cycle of the economic model, for all health states where:

a. **Instead of assuming a [redacted]L annual decline in FVC for placebo patients, the data for change in FVC from baseline from MOR-001 are used - please use the matched population from MOR-001 as requested in question A2. Please ensure that the annual data estimates available are used in the respective model cycle (instead of using the last measure of effectiveness in the study for every cycle of the economic model).**
    i. **Please consider extrapolating the FVC changes in the previous question to the model time horizon.**
b. **Instead of using the [redacted]% improvement in FVC associated with elosulfase, please use the FVC progression data captured in the ex-trial population in the matched MAA as per question A2. Please ensure that the annual data estimates available (for 10 years) are used in the respective model cycle for the first 10 years of the model (instead of using the last measure of effectiveness in the clinical study for every cycle of the economic model).**
    i. **Please consider extrapolating the 10-year time to FVC data in the previous question to the model time horizon.**

Include the impact of changes in FVC on mortality from baseline for every cycle and every health state of the model. Please note that if the impact of FVC decrease on

mortality remains that reported in the Neas and Schwartz, 1998 study, a conversion needs to be made from decrease in FVC L to FVC %.

Include the impact of changes in FVC on quality of life for every cycle and every health state of the model (by using the Lampe et al 2014 or other more appropriate source - please see question B17).

For matching patients from MAA ex-trial to MOR-001, please see the company response to A1 and A2.

[redacted]

For changing model structure from wheelchair status to FVC, please see the company response to B1 above. As outline in response to B1, FVC is an unreliable measure of patient endurance and functioning. This is further evidences in the original table 42 of the original submission (presented below).

Pearson's correlations between clinical measures change from baseline

Variables	6MWT	FVC	FEV1	uKS	EQ-5D	MPS-HAQ (Mobility domain)	MPS-HAQ (Self-care domain)
6MWT	[redacted]						
FVC	[redacted]	[redacted]					
FEV1	[redacted]	[redacted]	[redacted]				
uKS	[redacted]	[redacted]	[redacted]	[redacted]			
EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
MPS-HAQ (Mobility domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

MPS-HAQ (Self-care domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Values in bold are different from 0 with a significance level alpha = 0.05

As can be seen in the table above, FVC correlates very poorly with HRQoL (EQ5D). The current model structure, which is driven by wheelchair status correlates strongly with EQ5D. Thereby justifying the sensitivity and reliability of wheelchair status as clinically meaningful health sate to be used in the model.

Mortality assumptions based on FVC (or Quartel et al. 2018) has very limited impact on the model results. The company did a scenario analysis with making mortality assumptions (both based on FVC and Quartel et al. 2018) same in both arms of the model (treatment and SOC). The impact on QALY gain was less than [redacted]%. A scenario analysis with this assumption is presented below.

Table 26: Sensitivity analysis – same mortality assumptions in both SoC and treatment arms in the model

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

The original QALY gain in the company submission was [redacted].

B3. Priority question. Please explain how treatment discontinuation with elosulfase was estimated in the economic model (and point the ERG to the relevant calculations in the Excel model).

Please clarify if treatment discontinuation with elosulfase due to adverse reactions to the infusions was considered in the analysis.

No patients in the MAA stopped treatment or discontinued therapy due to adverse reactions and antibody titres were in line with previously published reports (Cleary et al., 2021, Hendriksz et al., 2016a, Schweighardt et al., 2015).

Model parameters

B4. Priority question. Please incorporate the clinical data requested for elosulfase and placebo patients in question A2, in the economic model (and provide a scenario analysis where the data from A1 is incorporated). Please make sure to use the available data on the progression of FVC, 6MWT and wheelchair dependency outcomes in the model.

Please use the year-1 and year-2 follow-up data from the MorCAP study to inform the transitions in the placebo arm of the model for cycle 1 and 2, respectively (please see question A4);

Please use the 10-year follow-up data from the ex-trial MAA population to inform the transitions in the elosulfase arm of the model for the first 10 cycles of the model wherever possible (please see question A4);

Please make any necessary assumptions (and explicitly document them) from year 3 onwards and year 11 onwards (please note the considerations made in question B2 to extrapolate data).

BioMarin's updated response (22/02/21): Please see response to A1 for matching of MOR-001 and MAA patients. For changing the health states from wheelchair use to FVC, please see response to B1 and B2.

For using Y1 and Y2 transitions of wheelchair use in MOR-001 (SOC arm), the results are presented in the table below.

Table 27: Wheelchair use transitions in MOR-001 Y1 and Y2

		From			
MOR-001 (baseline to Y1)		**No wheelchair use**	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]

	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

		From			
MOR-001 (baseline to Y2)		**No wheelchair use**	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Table 28: Wheelchair use transitions in MAA ex-trial patients

		From			
MAA-exTrial		**No wheelchair use**	**Some wheelchair use**	**Wheelchair dependent**	**Total n**
To	**No wheelchair**	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Yearly change in wheelchair status over 10 years for the MAA ex-trial is presented in the figure below. Please note that measurement for year 4 is missing.

Figure 8: Yearly change in wheelchair status over 10 years in the MAA ex-trial patients

Please note that MAA ex-trial wheelchair status was based on relatively small sample size of n=[redacted]. Any yearly breakup will be of limited value.

B5. Priority question. If the company does not provide the analyses requested in B4 (and in case the company's base case model structure is not changed), please provide the following analyses using the MorCAP and MAA data used in the submission:

Please use the year-1 and year-2 follow-up data from the MorCAP study to inform the transitions between wheelchair status in the placebo arm of the model for cycle 1 and 2, respectively;

Please use the annual data on change in wheelchair use for the nearly 3 years follow-up ERT-naive MAA elosulfase patients;

Please make any necessary assumptions (and explicitly document them) from year 3 onwards in the placebo and elosulfase arms of the model to estimate the changes in wheelchair dependency.

22/02/2021: Updated response below.

The model submitted by the company indeed uses wheelchair change 2 years data from MOR-001 for SOC arm and change in wheelchair from 2 (average follow-up of ERT naïve patients in MAA was [redacted] years) years of follow-up for ERT naïve patients from MAA for the treatment arm. These data are presented in the table below.

MOR-001 (baseline to Y1)		From			
		No wheelchair use	Some wheelchair use	Wheelchair dependent	Total n
To	No wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

MOR-001 (baseline to Y2)	From			
	No wheelchair use	Some wheelchair use	Wheelchair dependent	Total n

To	No wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Table 29: Wheelchair use transitions in MAA ERT-naïve patients

MAA-treatment naive		From			
		No wheelchair use	Some wheelchair use	Wheelchair dependent	Total n
To	No wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Some wheelchair	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Wheelchair dependant	[redacted]%	[redacted]%	[redacted]%	[redacted]
	Total n	[redacted]	[redacted]	[redacted]	[redacted]

Please note that n in Year 3 of ERT naïve patients from MAA was [redacted].

B6. Priority question. The ERG could not find the 16.5% improvement in FVC associated with elosulfase mentioned by the company on page 342 of the CS (reportedly taken from MOR-002/100 trial). Can the company please. Further clarification requested on 08/02/21:

a) **Point the ERG to the source and/or calculations used to arrive at this estimate. Please provide the unpublished data source and the calculations used to arrive at the [redacted]% estimate.**

b) **In case the company has not conducted the analysis requested in B2, please provide a scenario analysis in the model where this estimate is replaced with the FVC results captured in the ex-trial population in the matched MAA as per question A2. Similar to the request above, the ERG would like the company to use the annual FVC changes for every year of the economic model. This will not be given as transition probabilities but probability annual FVC values. Please make the same considerations as those noted in**

question B2 to extrapolate data beyond 3 years (ERT-naïve patients) and beyond 11 years (ex-trial patients).

BioMarin's updated response submitted on 22/02/21:

Regarding a), as responded to ERG on 02/02/2021, [redacted]% improvement in FVC comes from the MOR-100 CSR (attached MOR-100_CSR_report_body_only_final_26FEB20131). MOR-100 is the extension of MOR-002. This was part of the original submission to NICE in 2015. This can be further evidenced in the figure below from the MOR-100 CSR.

Figure b.1 (from MOR-100 CSR): Forced Vital Capacity versus Study Week Analysis Population: Intent-to-Treat

Note: Error bar refers to standard error.

Text from the technical report to the original submission of 2015 (to NICE) is presented below:

To reflect the impact of elosulfase alfa treatment on a Morquio A patients' mortality, a further adjustment was made to the calculated mortality rate of the untreated patient. Adjustment was based on an improvement factor derived from long term data from the MOR002/100 trial data showing a [redacted]% *improvement in FVC versus baseline over 3 years treatment with Elosulfase Alfa. The model uses the Bisection method to evaluate the Improvement factor.*

The change in FVC over the 10-year period for MAA- ex-trial patients was [redacted]% as presented in table 30 in previous response below. From all MAA Ex-trial patients with data assessment available, [redacted]% of patients improved in FVC compared to baseline (i.e., clinical trial baseline), [redacted]% were stable and [redacted]% declined in FVC.

Regarding b), as submitted by the company in its original response to ERG on 02/02/2021, this change will require structural change to the model. However, PSM matching of subjects for MAA and MOR-001 is now provided with this submission. Please see the annexure "PSM_Report_v3 20210211 [AIC]" submitted on NICE Docs.

Beyond the response to ERG on 02/02/2021, the company has conducted additional regression analysis and the results of that is in the annexure “RegressionAnalysis 20210212” submitted on NICE Docs. This analysis further strengthens the point that FVC correlates poorly with EQ5D. Thereby, there is very limited value in changing the model structure from wheelchair use to FVC.

Response submitted on 02/02/21:

[redacted]% improvement in FVC comes from the MOR-002 unpublished data. The change in FVC over the 10-year period for MAA- ex-trial patients was [redacted]% as presented in table below. From all MAA Ex-trial patients with data assessment available, [redacted]% of patients improved in FVC compared to baseline (i.e., clinical trial baseline), [redacted]% were stable and [redacted]% declined in FVC.

Table 30: Change in FVC over the 10-year period for MAA- ex-trial patients

	Ex-Trial Patients
FVC, L	
Mean (SD) at Baseline	[redacted] ([redacted])
Mean (SD) at Last Follow-up	[redacted] ([redacted])
Mean change, L (%)	[redacted] ([redacted])
95% Confidence Interval	[redacted], [redacted]
p-value	[redacted]

Number of Ex-Trial Patients	**n (% of total)**	**Range of percentual change from baseline**

Improvement in FVC change from baseline	[redacted] ([redacted]%)	[redacted]% <> [redacted]%
Stable in FVC change from baseline	[redacted] ([redacted]%)	[redacted]% <> [redacted]%
Decline in FVC change from baseline	[redacted] ([redacted]%)	[redacted]% <> [redacted]%

B7. Priority question. Please reconcile the differences (or explain these) in the data shown in Figure 25 of the CS and in the model spreadsheet "datasource" I13:M32 for the MOR-001 and the MAA ERT-naive patients' data.

Figure 25 in company submission (presented below) is based on MAA-treatment naïve patients. There were [redacted] patients in 'no wheelchair use' status at baseline. Of these at the end of follow-up ([redacted] data cut, mean follow-up [redacted] years), [redacted] remained on 'no wheelchair use', [redacted] moved to 'some wheelchair use' and [redacted] moved to 'always wheelchair use' health status.

Figure 2: Patients showing stability, decline, or improvement in wheelchair status over time versus baseline (based on MPS-HAQ Mobility Q33 and Q33a regarding wheelchair se)

Note: Only patients with available baseline and follow-up data are included in the change from baseline analysis.

Transition probabilities table presented in company submission (cost-effectivness model), spreadsheet “datasource” I13:M32 is prsented below.

Table 31: Transition probabilities used in the submission for treatment arm (MAA ERT-naïve)

MAA-treatment naive		Baseline		
		No use wheelchair	Some use wheelchair	Always use wheelchair
Last Follow-up	No use wheelchair	[redacted]	[redacted]	[redacted]
	Some use wheelchair	[redacted]	[redacted]	[redacted]
	Always use wheelchair	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]

For the standard of care arm, transition probabilities for the first 2 years are based on MOR-001 2-year follow-up data. Presented in the table below.

Table 32: Transition probabilities used in the submission for SoC arm (MOR-001)

MOR-001		Baseline		
Visit		No use wheelchair	Some use wheelchair	Always use wheelchair
2-year follow-up)	No use wheelchair	[redacted]	[redacted]	[redacted]
	Some use wheelchair	[redacted]	[redacted]	[redacted]
	Always use wheelchair	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]

For the subsequent years (2+ years), the transition probability calculations are shown below.

For the SOC arm (based on MOR-001), for 'no wheelchair use' and 'some wheelchair use', 6MWT annual decline in MOR-001 was used (7 metres and 7 metres). For 'wheelchair dependant' health state, annual decline in FVC of [redacted]L was used (based on MOR-001).

B8. Priority question. With regards to the categories of "non-responder"; "mild responder" and "long-term stabiliser" please clarify. Further clarifications requested on 08/02/21:

How these were used in the calculations included in the placebo arm of the economic model. Please give a detailed explanation of how these were used in transition probabilities or any allocation of patients throughout the model engine; The company has not provided any explanation on this.

How these were used in the calculations included in the elosulfase arm of the economic model. Please give a detailed explanation of how these were used in transition probabilities or any allocation of patients throughout the model engine; The company has not provided any explanation on this. The ERG asks that the company clarifies the rationale behind the assumption that everyone in the ESA arm are "long-term stabilisers" (or "improved wheelchair status" as the company mentioned in their reply) given that the data provided in Figure 8 below shows that all patients had a deterioration in their WC status.

If the percentage of "non-responders" in year 1 of the model for placebo was assumed to last for the remaining of the model; The company has not provided any explanation on this.

The difference in values between those reported in Table 77 of the CS and in the spreadsheet "datasource" O13:S32".

Clarification response submitted on 12/02/21:

Further to the text provided in the dossier (submitted to NICE and text of it from section 12.2.1 produced below), the company wants to provide the following clarification.

- Based on the MAA data, the multi-domain criteria (as labelled in the original submission to NICE in 2015) do not reflect the patient dynamic in terms of wheelchair use

- As an alternative, to define the long-term stabilization, in the current submission, change in wheelchair use for the Ex-trial patients has been used

- As there is no true baseline wheelchair use (In the clinical trial) for all Ex-Trial patients we used the change from MAA treatment naïve enrolment

- Based on this new analysis, Ex-Trial patients are stable or improve in the WC considering a mean treatment duration of ~8 years

- From this finding, in the base case 100% of patients are set as Long-term stabilizer, which results in a slower progression to health states as compared to Mild-decliner

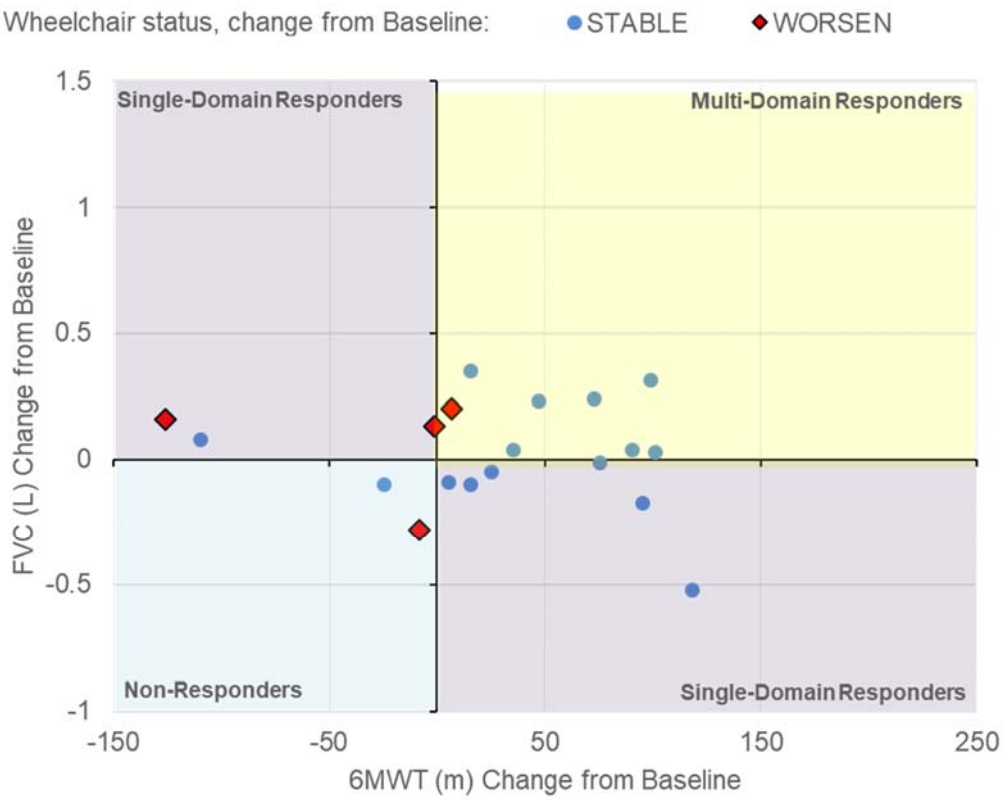
- We provided two scenario analysis in which 95% & 90% of patients being stable or improved. The scenario analysis is based on the number of patients who stop treatment in the MAA (section 12.5.13 in the dossier)

Further explanation is provided in section 12.2.1 and section 12.2.2 in the dossier and reproduced below.

Based on the long-term outcomes (up to 10 years) observed in the MAA clinical results, the multi-domain criteria proved not be an appropriated method to reflect the long-term dynamic of those patients as changes in either endurance and pulmonary function would not properly reflect the Wheelchair change, as observed in Figure and **Error! Reference source not found.** (in the dossier).

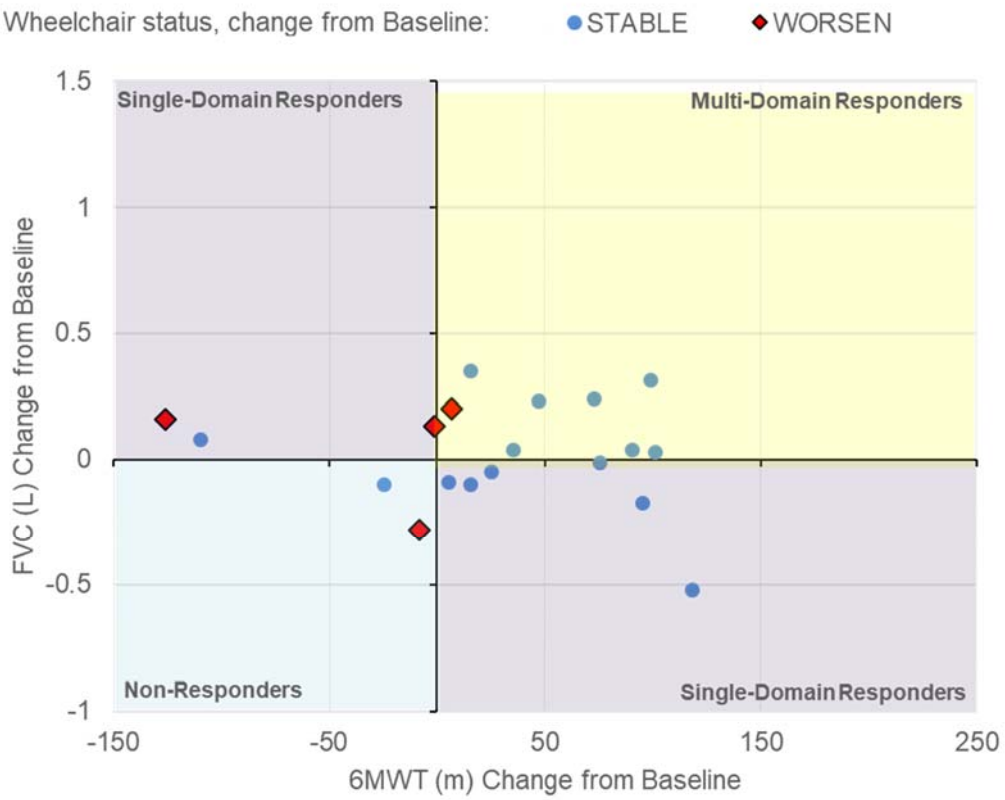
Based on the long-term findings from the MAA, an alternative concept is proposed, which would be based on the long-term Wheelchair change and which is described in item 12.2.2 of the dossier.

Figure 60 in the dossier: FVC change from baseline compared to 6MWT change from baseline and Wheelchair change. ERT Naïve patient, n=[redacted]



Only patients with baseline and follow-up assessment were included in the analysis. Multi-domain responders and single-domain responders are defined as the first submission (HST2 appraisal) and abovementioned.

Figure 60 from the dossier. FVC change from baseline compared to 6MWT change from baseline and Wheelchair change. ERT Naïve patient, n=[redacted]



Only patients with baseline and follow-up assessment were included in the analysis. Multi-domain responders and single-domain responders are defined as the first submission (HST2 appraisal) and abovementioned.

Text from section 12.2.2 below.

The MAA dataset provided a long-term view of the clinical outcomes of patients treated with elosulfase alfa for up to 10 years (Ex-trial patients, see section **Error! Reference source not found.**). Extrapolations were based mainly on the observed data from the patients in the MAA dataset. Patients treated for a mean treatment duration of 8.0 years (up to 10 years) are stable or improving in the Wheelchair Change, as of [redacted] patients improved the Wheelchair Status from 'Some use' to 'No use' and [redacted] patients improved from Wheelchair Dependent to 'Some use', comparing Wheelchair status at MAA enrolment versus last follow-up (Figure).

Figure 62 from the dossier. Ex-trial Patients dynamic chart: Boxed number represent number of patients moving across the Wheelchair status from the MAA enrolment date versus Last Follow-up.

[redacted]

The Wheelchair change results in the Ex-trial Patients sustain the long-term stability assumption of treated patients over untreated patients (Figure) and it is translated in the in the economic model as a proportion of patients achieving long-term stability (aka., ‘Long-term stabilizer’) or mild decline (aka., ‘Mild decliner’) after the initial 2 year cycle (

Table).

Figure 63 from the dossier. Patients showing stability, decline, or improvement in wheelchair status over time versus baseline (based on MPS-HAQ Mobility Q33 and Q33a regarding wheelchair se)

Table 88 from the dossier: Proportion of patients treated with elosulfase alfa achieving long-term stability in Subsequent Years after the two initial cycles

	Asymptomatic	No wheelchair use	Some wheelchair use	Wheelchair dependent	End stage
Long-term stabiliser	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Mild decliner	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Figure 8 from the dossier: Yearly change in wheelchair status over 10 years in the MAA ex-trial patients

[redacted]

Regarding the question on the percentage of “non-responders” in year 1, in the model, there is no patient set as non-responder for the placebo arm (only as mild decliner).

Further to the company response to B6, of all patients treated in the MAA (only [redacted] patient failed to meet the criteria) were either stable or improved, and scenario analysis with we provided two scenario analysis with 95% & 90% of patients being stable or improved.

Submitted on 02/02/21:

In the company submission, the starting population for the model is based on the MOR-001 baseline population which is used as a proxy of the prevalent population in England. The MOR-001 baseline population is representative of the worldwide prevalent population and their WC status which was captured by the MPS HAQ (Table below). Asymptomatic patients where patients less than 3 years old who reported not using WCs or mobility aids. The reference population for the evaluation reflects all MPS IVA patients who would be eligible to receive elosulfase alfa as per the approved licensed indication.

Table 33: Starting health state for the MPS IV population

Health State	Proportion of patients
Asymptomatic	5%
Symptomatic (does not use a WC)	48%
Sometimes use WC	34%
Always use WC	13%
Paraplegic	0%
Pre-death	0%

Source: (P. Harmatz et al. 2013)

Responder analysis

Given the multi-systemic nature of MPS IVA disease, patients treated with elosulfase alfa are likely to respond across several outcomes and may see improvement in one domain and stabilization or deterioration in another. This treatment effect would likely translate into clinically meaningful benefits to patients with Morquio A, given the unrelenting progressive nature of the disease across multiple domains. Hence to determine the proportion of patients with a treatment effect, a responder analysis was undertaken in the per protocol population of the MOR-004/MOR-005 pivotal trial at week 72 to assess the impact of treatment across the two main domains, endurance (as measured by 6MWT and 3MSCT) and pulmonary function (as measured by FVC and MVV).

Responders were defined as patients with a positive change from baseline (improvement) in either endurance or pulmonary function. **Long-term stabilisers** were those patients with improvements in both endurance and pulmonary function. While **mild decliners** were defined as those with improvements in either endurance or pulmonary function. At week 72, all patients in the per-protocol population were either **mild decliners** or **long-term stabilisers** which indicates that all these patients had a positive treatment effect.

At week 72, 72.7% (24 out of 33) of patients were **long-term stabilisers**, while the remaining 27.3% (9 out of 33) of patients were mild decliners (table below), there were no patients who did not show an improvement in either domain.

Table 34: Summary of 6MWT results from MOR-004 (ITT)

6-minute walk test (metres)	Placebo (N=59)	Elosulfase alfa 2.0mg/kg/week (N=58)	Difference
Baseline			
N	59	58	
Mean (SD)	211.9 (69.9)	203.9 (76.3)	
Median	228.9	216.5	
Min, Max	36.2, 312.2	42.4, 321.5	
Week 24 change from baseline			
N	59	57	
Mean (SD)	13.5 (50.6)	36.5(58.5)	22.5m (95% CI 2.9,43.1)
Median	9.9	20.0	
Min, Max	-99.2, 220.5	-57.8, 228.7	

Source: (Christian J. Hendriksz, Burton, et al. 2014)

Using the primary analysis ANCOVA model, the least square mean (± SD) changes in 6MWT and FVC from MOR-004 Baseline for long-term stabilisers at Week 72, were 60.9m (±67.16m) and 15.6% (±21.81%) respectively (table below). The least square mean (± SD) changes in 6MWT and FVC from MOR-004 Baseline for mild decliners at week 72, were 0.1m (±64.74m) and -4.6% (±9.91%) respectively. In conclusion these responder analysis results show that all subjects receiving the weekly regimen from the start of MOR-004 who did not have surgery (per-protocol population) had a positive treatment effect with improvements in either endurance or pulmonary function

Table 35: Frequency Counts of Response on Endurance and Breathing from Baseline to on study (per protocol population; QW/QW Cohort)

Analysis time point	Category	Number of Subjects	Percentage (%)
Week 24 (MOR-005 Baseline)	Multi-domain responder[a]	33	67.4
	Single-domain responder[b]	15	30.6
	Non-responder[c]	1	2.0
Week 48 (MOR-005 Week 24)	Multi-domain responder[a]	17	85.0
	Single-domain responder[b]	3	15.0
	Non-responder[c]	0	0
Week 72 (MOR-005 Week 48)	Multi-domain responder[a]	24	72.7
	Single-domain responder[b]	9	27.3
	Non-responder[c]	0	0

The model assumes patients follow a certain pathway with progression through the model determined by their current health state. Progression through the model is based on four different outcome measures.

1. **Time to symptom development**: This outcome measure is applicable in all cycles to patients in the "asymptomatic" health state only. "Asymptomatic" patients would progress to the "no WC" health state when they reach the age of 3, by which point they would have developed clinical manifestations of the disease leading to endurance limitations and musculoskeletal complications (Montaño et al. 2007).

2. **Change in WC use:** This outcome is not applicable to patients in the Early Stage health state. For all other health states, patients have the chance of moving from one wheelchair use state to another, based on the observed changes in WC status (WC shift data) from baseline to week 120 of the MOR-005 clinical study and MOR-001 natural history study as captured by the MPS HAQ questionnaire (Questions 33 and 33a).

Table 36: Wheelchair progression in patients with MPSIVA in MOR-005 versus untreated patients from the MOR-001 study

MOR-005 120-week data			
Baseline	No WC	Sometime. WC	Always WC
No WC	[redacted]%	[redacted]%	[redacted]%
Sometime. WC	[redacted]%	[redacted]%	[redacted]%
Always WC	[redacted]%	[redacted]%	[redacted]%
MOR-001 (based on 2-year data)			
Baseline	No WC	Occ. WC	Always WC
No WC	82%	18%	0%
Sometime. WC	4%	76%	20%
Always WC	0%	22%	78%

Following treatment, patients' WC status would either improve (reduced WC dependency), stabilize (maintained the level of WC dependency) or worsen (increased WC dependency). Patients whose WC status improved had a corresponding backward shift reflecting the reduced WC dependency. Those whose WC status stabilized remained in the same WC health state. While patients who worsened, progressed to the next health state in relation to the increased level of WC dependency. Based on clinical opinion, a proportion of patients whose WC status worsens would discontinue elosulfase alfa treatment after two cycles of the model due to treatment non-response. All other patients would continue treatment with elosulfase alfa.

An analysis of the data from the English MAA shows that patients are stable over time in terms of wheelchair use. This data has patients who have been on therapy up to ten years and shows a similar pattern to the pivotal trial data where the vast majority of patients do not appear to deteriorate. The data from the real world, unlike the trial data also shows improvements for those patients in the Always use wheelchair status. This data will be used as a sensitivity analysis.

Table 37: English MAA wheelchair data

English MAA-ERT naive data – Average treatment duration [redacted] years			
Baseline	No WC	Sometime WC	Always WC
No WC	[redacted]%	[redacted]%	[redacted]%

Sometime WC	[redacted]%	[redacted]%	[redacted]%
Always WC	[redacted]%	[redacted]%	[redacted]%

3. **6MWT:** This outcome measure is applicable for the 2nd cycle onwards for patients in the "no WC" and "sometimes WC" health states. Untreated patients would progress based on a 6.84 meters annual decline in their 6MWT until they reach the "WC dependent" health state. This is based on 2 year longitudinal data from the MOR-001 study which showed progressive annual decline in 6MWT in MPS IVA patients.

4. **FVC:** As patients in the "WC dependent" and "paraplegic" health states may be unable to perform the 6MWT, disease progression through the model for all patients is based on a [redacted]L decline in their FVC. This is based on clinical opinion that MPS IVA patients see a progressive decline in their pulmonary function once they have stopped growing due to progressive worsening of restrictive and obstructive lung disease. This is a conservative assumption for treated patients, who have shown a maintenance of their lung function over time.

Average 6MWT scores were assigned to the no WC and sometimes WC health states. This was based on the mean 6MWT scores of all patients who reported not using WC and using WC sometimes at baseline in the MOR-001 natural history study respectively (See table below). Similarly, average FVC score was assigned to the WC dependent and paraplegic health states based on mean FVC of patients who reported always using WCs at baseline in the MOR-001 study.

Table 38: Average 6MWT and FVC values per wheelchair group in MOR-001 study

	No WC	Sometimes uses WC	Always uses WC
6MWT (m)			
Mean	[redacted]	[redacted]	[redacted]
95% CI	[redacted] – [redacted]	[redacted] – [redacted]	[redacted] – [redacted]
FVC (L)			
Mean	[redacted]	[redacted]	[redacted]
95% CI	[redacted] – [redacted]	[redacted] – [redacted]	[redacted] – [redacted]

Exit 6MWT values were assigned to the no WC use and sometimes use WC health states based on the upper 95% CI of the health state they would exit into. Based on clinical opinion from clinical experts an exit FVC score of [redacted]L was assigned to the "WC dependent" and

"paraplegic" health states. As patients would require mechanical ventilation when their FVC is 0.5L or less and as such transition to the pre-death health state (table below).

Table 39: Mean and exit scores for wheelchair health states

Health State	**Value**	**Unit**	***Source***
Never use WC			
Annual average loss in 6 Minute Walk Test	6.84	m	*MOR-001*
Mean score for patients in this health state	289	m	*MOR-001*
Exit Score for transition to Sometimes use WC health state	207	m	*MOR-001*
Sometimes use WC			
Annual average loss in 6 Minute Walk Test	6.84	m	*MOR-001*
Mean score for patients in this health state	180	m	*MOR-001*
Exit Score for transition to Always WC health state	46	m	*MOR-001*
Always use a WC health state			
Mean FVC level for patients in this health state	1.0	L	*MOR-001*
Average annual loss in FVC measure	0.1	L	*Clinical Opinion*
Exit FVC level for transition to Pre-death health State	0.5	L	*Clinical Opinion*

Patients in all health states except pre-death health state would be eligible for treatment with elosulfase alfa. Based on evidence from the pivotal trial and extension study (MOR-004/005), long term experiences from similar MPS disorders and clinical opinion, we have assumed that treatment of MPS IVA patients with elosulfase alfa would lead to the following modelled benefits:

Delay the development of musculoskeletal complications by up to 5 years:

This is based on clinical opinion the delay in developmental of symptoms seen in asymptomatic MPS I, II and VI patients initiated on ERT is an MPS class effect which would be also seen in asymptomatic Morquio A patients treated with elosulfase alfa. This is also supported by evidence from several sibling case studies in MPS I, II and VI patients, which showed that younger siblings initiated on therapy whilst asymptomatic did not develop significant clinical manifestations of their disease such as musculoskeletal complications, cardiac disease and corneal clouding after up to 10 years of ERT treatment. However at the equivalent age, the older sibling with the same disease phenotype already had these complications well established. Clinical opinion is that this is an MPS class effect and that

treatment of asymptomatic Morquio A patients with elosulfase alfa would delay the development of musculoskeletal complications by 5 years.

Reduction in WC dependency and WC progression based on WC shift data:

A comparison of WC shift patterns from Week 120 MOR-005 results and MOR-001 over a similar time frame shows that treatment of Morquio A with elosulfase alfa leads to a reduction in WC use and a reduced rate of disease progression (table below).

Table 40: Wheelchair progression in patients with MPS-IVA in MOR-005 versus untreated patients from the MOR-001 study

MOR-005 120-week data			
Baseline	No WC	Sometime. WC	Always WC
No WC	[redacted]%	[redacted]%	[redacted]%
Sometime. WC	[redacted]%	[redacted]%	[redacted]%
Always WC	[redacted]%	[redacted]%	[redacted]%
MOR-001 (based on 2-year data)			
Baseline	No WC	Occ. WC	Always WC
No WC	[redacted]%	[redacted]%	[redacted]%
Sometime. WC	[redacted]%	[redacted]%	[redacted]%
Always WC	[redacted]%	[redacted]%	[redacted]%

Improved health utility per health state:

For each health state, patients treated with elosulfase alfa have higher utility values than those on standard care. The increased utility values are based on results from a subset of patients in the PRO studies with clinical outcomes recorded, which showed a strong positive correlation between patient's 6MWT and FVC with their health related quality of life, as measured by the EQ-5D (Lampe et al. 2014b). This showed that for every 10 metres gained in the 6MWT there was a 0.02 increase in utility. Thereby, indicating that improvement in 6MWT and FVC seen with elosulfase alfa would translate into improved quality of life.

The utility for each health state for elosulfase alfa treated patients is increased in accordance to the difference in the clinical outcomes (6MWT or FVC) between elosulfase alfa treated patients and standard care treatment.

The model basecase does not consider potential utility gains outside of the 6MWT and FVC improvements. However, there is evidence that some patients treated with elosulfase alfa experience benefits beyond these functional measures, including a decrease in pain, corneal clouding, and sleep difficulties, and an improvement in wrist function and hearing (ID744 2015)

(Hughes et al. 2019). The model considers the following improvements as a sensitivity analysis.

- Pain 0.059 (Suponcic et al. 2012 (Suponcic, Dibonaventura, and Victor 2012), indicating that a 1 point reduction in pain intensity related to a 0.025 utility gain in general public.

- Visual acuity 0.09 (Brown et al. 2003 (Brown et al. 2003), indicating that improvement in visual acuity was between 0.07 and 0.11)

- Sleep difficulties 0.10 (Leger et al. 2012 (Leger et al. 2012), indicating a 0.10 difference in utility between chronic insomnia and those without insomnia)

- Wrist function 0.10 (Cavaliere and Chung 2010 (Cavaliere and Chung 2010), indicating a 0.10 improvement in wrist function between limited and intact residual wrist function)

- Hearing 0.019 (Carter and Hailey 1999 (Carter and Hailey 1999)), indicating a 0.019 utility improvement due to cochlear implant in those who were partially deaf.

Stabilization of disease progression:

Given the cost of elosulfase alfa, it is unlikely that patients would remain on the drug if their disease continues to progress at the same rate prior to treatment. Hence we have assumed that patients whose progression rate is not reduced would discontinue treatment. We have termed these patients ‘non-responders’.

Experiences from other MPS disorders such as MPS VI suggests that treatment would elosulfase alfa would lead to a halting of disease progression in majority of patients. In a 10 year follow-up study of 117 Maroteaux-Lamy syndrome (MPS VI) patients, patients treated with galsulfase for a duration of 7.3 years had maintained a statistically significant increase in FVC (29.3%) and 6MWT (21.1%) over their baseline function and also showed no further degradation of cardiac function (R. Giugliani et al. 2014).

Hence the model assumes that after initial improvement due to treatment, there would be three groups of patients, ‘*Improved wheelchair status*’, ‘*Stabilisation*’ and ‘*Worsened wheelchair status*’ based on the following definition. Please note that these 3 subsets were wrongly labelled as ‘long-term stabiliser’, ‘mild decliner’ and ‘non-responders’ in the company submission (cost-effectiveness model).

- *Improved wheelchair status:* these are patients who see a stabilization of disease due to continuous response to elosulfase alfa treatment. These patients would remain on treatment.

- *Stabilisation:* these are patients who treatment with elosulfase alfa would lead to a reduced rate of disease progression compared to untreated patients. These patients would remain on treatment

- *Worsened wheelchair status:* these are patients who elosulfase alfa would not change the rate of disease progression. These patients would discontinue treatment.

Clinical opinion is that the proportion of improved wheelchair and stabilisation status patients would vary according to WC health states and would depend on how much irreversible damage is already present when patients start treatment. The proportions of improved wheelchair and stabilisation status patients are detailed below:

- No WC use health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%

- Some WC use health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%

- WC dependent health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%

- Paraplegic health state: improved wheelchair: [redacted]%; stabilisation: [redacted]%

Clinical opinion was that the rate of disease progression in stabilisation patients would be 30% of that of untreated patients (i.e. 6MWT would decline at 2.1m per annum instead of 7.1m).

Delay in surgery and faster recovery rates:

Evidence from the MOR004/005 clinical trial showed that treatment with elosulfase alfa led to a [redacted] in time to orthopedic surgery. As such the costs and outcomes of the surgery, including the utility decrement are discounted proportionally to reflect this delay.

Based on clinical opinion, treatment with elosulfase alfa would result in faster recovery rates compared to untreated patients. This is due to the improved health of elosulfase alfa treated patients at the time of surgery compared to untreated patients.

Surgery

In each health state a proportion of patients would undertake 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 complication leading to paraplegia or death. Patients who become paraplegic will enter the “Paraplegic ” health state.

Although some patients might have the same surgeries, given the infrequency of this occurrence the model assumes patients would have not repeat the same surgery in the same health state. After surgery patients enter a recovery period during which they have a reduced quality of life. After this recovery period has elapsed, they would return back to the same health state.

The type and proportion of surgeries per health state; rates of surgical complications; duration and utility decrement of recovery period are based on the UK expert-reported surgical frequency (See tables below).

Table 41: Proportion of patients undergoing surgery in each health state in MOR-005

Surgery	Early stage	No use a wheelchair	Sometimes use wheelchair	Wheelchair dependent
Cervical Fusion Operation	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Genus Valgum surgery	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Spinal decompression surgery	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Hip surgery	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Lower spine surgery	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Aortic valve replacement	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Tonsillectomy	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Ear tube placement	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Corneal replacement	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Cataract surgery	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Gastrectomy	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Table 42: Surgical outcomes in MOR-005

Surgery	Successful	Paraplegic	Death

Cervical Fusion Operation	[redacted]%	[redacted]%	[redacted]%
Genus Valgum surgery	[redacted]%	[redacted]%	[redacted]%
Spinal decompression surgery	[redacted]%	[redacted]%	[redacted]%
Hip surgery	[redacted]%	[redacted]%	[redacted]%
Lower spine surgery	[redacted]%	[redacted]%	[redacted]%
Aortic valve replacement	[redacted]%	[redacted]%	[redacted]%
Tonsillectomy	[redacted]%	[redacted]%	[redacted]%
Ear tube placement	[redacted]%	[redacted]%	[redacted]%
Corneal replacement	[redacted]%	[redacted]%	[redacted]%
Cataract surgery	[redacted]%	[redacted]%	[redacted]%
Gastrectomy	[redacted]%	[redacted]%	[redacted]%

B9. Priority question. The ERG could not find the evidence used by the company on the delay in surgery associated with elosulfase referred by the company on page 350 of the CS (source MOR-004/005). Please can the company provide the data used to estimate the 4-month delay parameterised in the model?

Delay in surgery for ERT treated patients comes from MOR-004/005. This is listed as figure 14.2.6 in the CSR submitted by the company. A conservative assumption of [redacted] delay in surgery on treatment was used in the model.

Figure 3: Time to orthopaedic surgery in MOR-004/005 (Figure 14.2.6 in MOR-005 CSR) (BioMarin, 2017)

However, it may be noted that time to delay in surgery has very limited/ no impact on the model ICER results in the company submission. With time to delay in surgery made to 0, the ICER remains same. Table of result presented below.

Table 43: Sensitivity analysis – Impact of time to delay in surgery on ICER for SoC

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]

B10. Priority question. Please provide a scenario analysis where patients entering the model (i.e starting treatment with elosulfase or best supportive care) are either in the asymptomatic stage (4.9%) or in the no wheelchair use (95.1%) to reflect the clinical expert opinion provided to the ERG that in current clinical practice all patients would start treatment in one of these health states.

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 44: B10 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	

No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B11. Priority question. Please provide a scenario analysis where the 5-year delay in transition from the 'asymptomatic' state to the 'no wheelchair use' in the elosulfase arm of the model is removed.

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 45: B11 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B12. Priority question. From a quick inspection of the "PF_" tabs in the model (i.e. patient flow in the treatment and placebo arms), it seems to the ERG that the wrong RR of death is being used in some of the calculations in the elosulfase tabs. For example, the calculations in sheet "PF_treatment-Asy", column EA are using a RR of death of 2.38. This was encountered in several other columns and tabs. Can the company please clarify if this is a mistake and correct all the relevant tabs and calculations where needed. Further clarification requested on 08/02/21: Please can the company clarify (and correct the mistake if necessary) why patients receiving treatment (i.e. in the different "PF_treatment…" tabs of the model) incur a 2.38 RR of

death applied to the general population, when the CS describes that patients on treatment have the same mortality as the general population.

Submitted on 12/02/21:

As explained in the response to ERG on 02/02/2021, the RR of death has very limited impact on the overall ICER. The company realises that applying a RR to the treatment arm may be double counting the risk. The company did a scenario analysis with making mortality assumptions (both based on FVC and Quartel et al. 2018) same in both arms of the model (treatment and SOC). The impact on QALY gain was less than 1%. A scenario analysis with this assumption is presented below.

B12 scenario analysis results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

The original QALY gain in the company submission was [redacted].

Submitted on 02/02/21: The company looked at the relative risk of death reference in "PF_treatment-Asy", column EA of the submission. Although this is not a mistake, the company realises that this may be double counting the risk of death. The company did a scenario analysis with making mortality assumptions (both based on FVC and Quartel et al. 2018) same in both arms of the model (treatment and SOC). The impact on QALY gain was less than [redacted]%. A scenario analysis with this assumption is presented below.

Table 46: B12 scenario analysis results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

The original QALY gain in the company submission was [redacted].

B13. Priority question. Please include a scenario analysis in the model where the proportion of patients receiving surgery for each health state is that reported in the table below.

Surgery	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent

Cervical Fusion Operation	0%	37.5%	37.5%	0.0%
Genu Valgum surgery	0.0%	0.0%	41.0%	0.0%
Spinal decompression surgery	0.0%	0.0%	40.0%	0.0%
Hip surgery	0.0%	17.5%	17.5%	17.5%
Lower spine surgery	0.0%	23.0%	17.5%	0.0%
Aortic valve replacement	0.0%	15%	10%	15.0%
Tonsillectomy	43.0%	15%	0.0%	0.0%
Ear tube placement	36.0%	15%	0.0%	0.0%
Corneal replacement	0%	0.0%	0.0%	0.0%
Cataract surgery	0%	0.0%	3.4%	3.4%

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 47: B13 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B14. Priority question. Please include a scenario analysis in the model where elosulfase alfa-treated patients have the same recovery rates from surgery as untreated patients.

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 48: B14 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B15. Priority question. Please clarify if all the MOR-001 data used in the economic analysis was that of the matched population to the MOR-005 patient characteristics, and please confirm if the Excel folder shared with the ERG on 15th December named "Table 74 - Ad-hoc analysis" is based on MOR-001 data matched to the MOR-005 population. Further clarification requested on 08/02/21: The ERG simply requires clarification (i.e. a yes or no answer) if the MOR-001 data currently used in the model for the comparator arm is that of the matched population to the MOR-005 characteristics or the entire population in MOR-001.

Company's response submitted on 12/02/21: No. This has not been matched (MOR-001 vs. MOR-005).

Submitted on 02/02/21: For matching of MOR-001 with MOR-005, please see response to A5 (presented below again).

Baseline characteristics of MOR-001 and MOR-004 is presented in the table below.

Table 49: Baseline characteristics of MOR-001 and MOR-004

	MOR-001	**MOR-004 (2mg/kg QW)**
3MSCT		
n	88	56
Mean (SD)	31.3 (17.5)	30.1 (16.2)
p value		0.680
6MWT (m)		
n	97	56
Mean (SD)	207.8 (84.3)	209.4 (71.8)
p value		0.905
uKS		
n	97	56
Mean (SD)	33.5 (25.6)	27.2 (14.2)
p value		0.092

*unpaired 2 sample t-test

For more details on MOR-005, please refer to Table 37 in the original submission. As can be seen in the table above, these 2-patient cohort (MOR-001 and MOR-005 2mg/kg QW) had baseline characteristics very similar, with all p value >0.05.

Further comparison of MOR-001 and MOR-005 for QW-QW cohort was presented in Table 51 in the original submission by the company and is presented in the table below.

Table 50: MOR-005 long term follow-up for 6MWT in the MPP QW QW population

	Year 1[a]		Year 2[b]	
	MOR-001	QW-QW	MOR-001	QW-QW
MPP Population/MOR-001				
6MWT (m), N	67	43	[redacted]	[redacted]
LS mean change from baseline[c] (SE)[d]	-6.7 (8.78)	38.5 (11.02)	[redacted]	[redacted] ([redacted])
P-value[e] for difference from MOR-001		0.0016	[redacted]	[redacted]

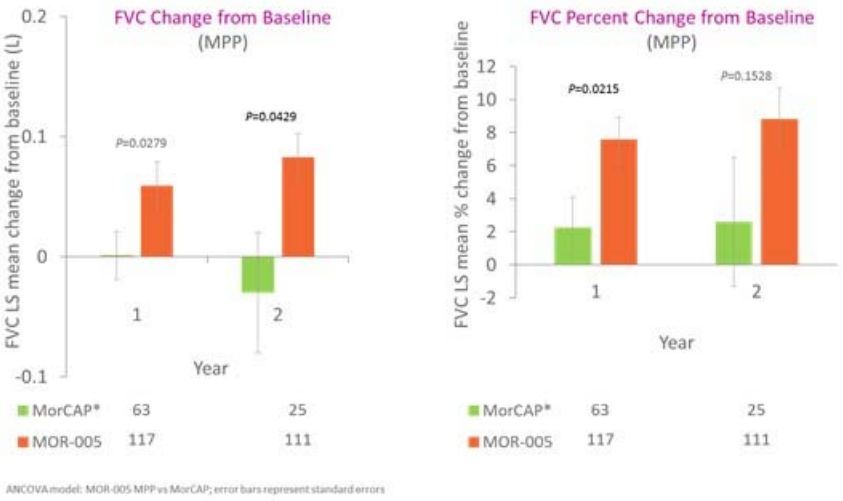
[a]Year 1 represents data collected from the MOR-004/005 Week 72 assessment and the MOR-001 Year 1 follow-up window

[b]Year 2 represents data collected from the MOR-004/005 Week 120 assessment and the MOR-001 Year 2 follow-up

[c]Baseline LS means are based on ANCOVA of baseline measurement with model terms treatment age group, and 6MWT distance category
[d]LS mean changes based on repeated measures ANCOVA model including treatment, time point, treatment and time point interaction, age group, and baseline 6MWT category, and baseline measurement (3MSCT and uKS only)
[e]P-value determined by t-test and the repeated measures ANCOVA model
LS: least square; SE: standard error

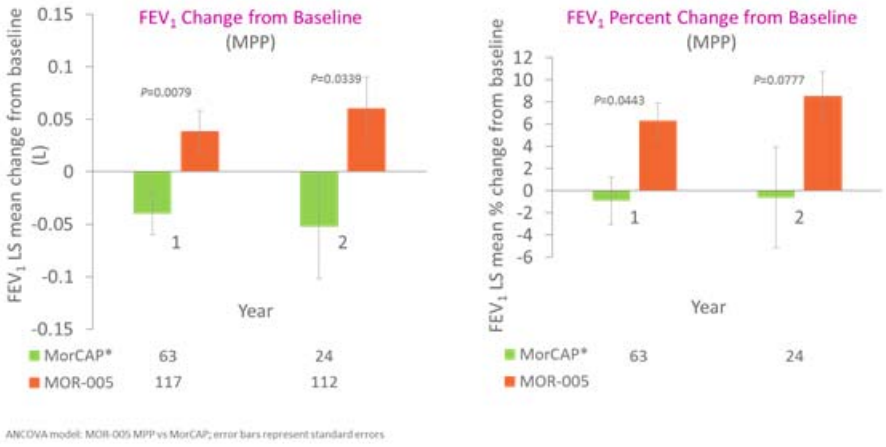
The company original submission (Figure 34 and 35) also present comparison of FVC and FEV1 in MOR-001 and MOR-005 and is shown in the figure below.

Figure 4: MOR-005 FVC change from baseline and percent change from baseline compared to MOR-001



Source: (Hendriksz et al., 2016a)

Figure 5: MOR-005 FEV1 change from baseline and percent change from baseline compared to MOR-001



Source: (Hendriksz et al., 2016a)

However, the company will conduct feasibility analysis of doing a PSM (it may be noted that MOR-001 had a short follow-up of 2 years). But this will not be possible before 2nd of February 2021 (deadline for response). The company proposes to investigate gender, age, ethnicity, genotype, height (not in MAA), weight, uKS, 6MWT, FEV1/FVC as covariates in the PSM. Clinical opinion will be sought before embarking on any such matching variables. Company will send the timelines separately for this analysis.

B16. Please clarify if there are more recent sources available to model the impact of FVC reduction on mortality (rather than the 1998 study used by the company in the model). If so, please provide a scenario analysis using these more contemporary data.

Mortality assumptions based on FVC (or Quartel et al. 2018) has very limited impact on the model results. The company did a scenario analysis with making mortality assumptions (both based on FVC and Quartel et al. 2018) same in both arms of the model (treatment and SOC). The impact on QALY gain was less than [redacted]%. A scenario analysis with this assumption is presented below.

Table 51: B16 scenario analysis results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

The original QALY gain in the company submission was [redacted]

Health related quality of life

B17. Priority question. The company mentions Lampe et al 2014 to justify an increase in utility of 0.02 for every 10 meters gained in the 6MWT as well as the 0.20 increase in utility for every 1L improvement in FVC. However, the ERG could not find any of these estimates in the study mentioned. Please confirm the source used to obtain these values and provide any calculations needed to arrive at the estimates. In their response the company references Lampe et al 2014b, but does not provide this reference. Please can the company send us the full reference for this paper.

Company's response on 12/02/21: A copy of the full reference has been uploaded on NICE Docs.

Lampe et al. 2014b investigates the relationship between clinical outcomes and patient-reported outcomes in 24 German patients with Morquio A aged ≥ 7 years. The results of the correlation analysis showed that there was a strong and statistically significant correlation between the endurance outcome of 6MWT and EQ-5D HRQoL utility score across patients: R=0.713 (p=0.0019). Furthermore, the authors report that an increase of 100 meters in the 6MWT distance is associated with a 0.2 increase in the EQ-5D utility score (page 3 of Lampe et al. 2014b).

The study also reports Regression Analysis between Endurance and Pulmonary Function Measures and Height and the Patient's EQ5D-5L/Health-Related Quality of Life. Pearson's

Sample size (n), coefficient (r), Coefficient of Determination (Adjusted R^2), p value and slope of the line presented in table 2 of the publication (snapshot of the table is presented below), shows that FVC strongly correlates with EQ5D score, with slope of the line being 0.2

(indicating that every 1L increase in FVC is associated with 0.2 increase in EQ5D utility score.

Figure 6: Pearson Correlation and Regression Analysis between Endurance and Pulmonary Function Measures and Height and the Patient's EQ5D-5L/Health-Related Quality of Life

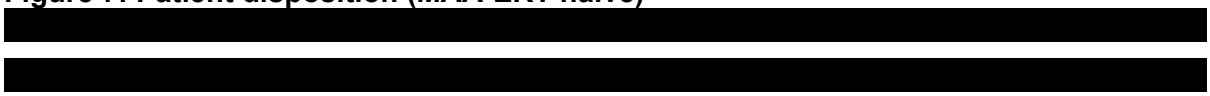
B18. Priority question. In sheet "Utilities", the natural history annual decrease (Utilities!C25) is added to the 'new assumption' - increase in 6MWT (Utilities! C24). Furthermore, this decrease is listed as an increase on the Main_Source_Update sheet. Please clarify whether this estimate is an increase or decrease and provide the rationale for using these values.

The 6MWT labelled in the original company submission (cost-effectiveness model sheet "Utilities") as increase indeed should be decrease in 6MWT. The figure presented in figure 2 of Clearly et al., shows an extrapolation of MOR-001, and shows a decrease of 50.6 over a 10-year period.

B19. Priority question. Please provide more information around the mean utility estimates derived from the MAA quality of life data analysis. More specifically, please explain how utility values were estimated for the different wheelchair states, for both treatment arms and provide details for what time point they were collected in the MAA dataset, which patient group and the methods of calculating them (please provide measures of statistical significance between baseline and end of study values).

The utility values for each state of wheelchair use was calculated from MAA ERT naïve patient dataset. At the [redacted] data cut there were [redacted] patients, with [redacted] exTrial and [redacted] ERT naïve. Of these [redacted] ERT naïve patients there were [redacted] patients for who EQ5D data was available at the last follow-up. Of these [redacted], [redacted] patients had both baseline and last follow-up data for EQ5D. Patient disposition is shown in the figure below.

Figure 7: Patient disposition (MAA-ERT naïve)



The baseline and last follow-up EQ5D values for these [redacted] patients is presented in the table below.

Table 52: Baseline and last follow-up EQ5D values and their wheelchair status in MAA

The EQ5D mean utility values by wheelchair status at both baseline and last follow-up is presented in the table below.

Table 53: Mean (SD) EQ5D utility values in MAA ERT-naïve patients

MAA-ERT naive	Mean score (EQ-5D) @ Baseline			Mean score (EQ-5D) @ Last Follow-up		
	No WC use (n=[redacted])	Some use WC (n=[redacted])	Always use WC (n=[redacted])	No use WC (n=[redacted])	Some use WC (n=[redacted])	Always use WC (n=[redacted])
EQ-5D	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
p value (unpaired t-test)				[redacted]	[redacted]	[redacted]

B20. Priority question. Please provide a scenario analysis removing the FVC- and 6MWT- related adjustment (i.e. the utility increments used in the elosulfase arm) and using the same mean utility values in both arms of the model.

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 54: B20 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B21. Priority question. Please change the range used (the assumed +/- 10%) to vary the mean utility values in the probabilistic sensitivity analysis to reflect the 95% CIs of the mean estimates derived from the MAA data.

The 95% confidence intervals of the mean estimates are provided in the table below. The probabilistic sensitivity analysis assumptions were updated in the economic model submitted along with this document.

Table 55: B21 probabilistic sensitivity analysis

Variable	**Base Case Value**	**95% Confidence Interval**	
		Lower Case Value	Upper Case Value
Untreated: No wheelchair use utility	[redacted]	[redacted]	[redacted]
Untreated: Sometimes use wheelchair utility	[redacted]	[redacted]	[redacted]
Untreated: Wheelchair dependent utility	[redacted]	[redacted]	[redacted]
Treated: No wheelchair use utility	[redacted]	[redacted]	[redacted]
Treated: Sometimes use wheelchair utility	[redacted]	[redacted]	[redacted]

Treated: Wheelchair dependent utility	[redacted]	[redacted]	[redacted]

B22. Priority question: Please provide a scenario analysis using the utility estimates from the original submission (HST2).

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 56: B22 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B23. Priority question. Please explain why a systematic literature search was not undertaken to identify the impact of surgery on patients' quality of life. In particular, the 0.25 utility decrements applied to some of the surgeries appear to be quite high without further justification. Please validate the surgical utility decrements used in the model with evidence from the literature.

The systematic literature search was not undertaken. However, the surgery utility data comes from clinical experts (England) as provided in both original and new submissions and has been used in other NICE appraisals for other ERTs (NICE, 2018).

B24. Priority Question. Were the estimates provided in table 90 of the CS used in the model's scenario analysis around the surgical utility decrement?

The figures reported in Table 90 of the CS were not used directly in the model for the surgical utility decrement. A Utility Decrement based on UK expert clinical opinion is used in the model as provided in Table 86 of the CS.

Costs and resource use

B25. Priority question. Please provide a scenario analysis using the following estimates for resource use.

Resource	Visits per cycle (1 year)					
	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent	Paraplegic	End Stage
Non-Hospital						
Visit to GP	0	0	0	0	0	0
GP Nurse visit	0	0	0	0	0	0.0
Hospitalisation						
Specialist visit	1.9	2.1	3.2	4.3	6.2	6.2
Accident & Emergency Visit	0.0	0.0	0.0	0.3	0.3	0.0
Pulmonary specialist visit	1	1	1	1	1	1
Pain Management Specialist Visits	0	0	0	0	0	4
Mental Health Specialist Visits	1	1	1	1	1	1
Cardiology Specialist Visits	1	1	1	1	1	1
Ophthalmology	1	1	1	1	1	1
ENT Specialist Visits	1	1	1	1	1	1
Palliative care	0	0	0	0	0	4
Other						

Ventilation*	0.0	0.0	0.0	0.0	0.0	1.0

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 57: B25 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B26. Priority question. Please provide a justification for the administration cost included in the model. More specifically:

a) Has this cost been updated to the current year?

b) How was the per cycle cost calculated?

c) Why was the 2013/14 cost chosen when this tariff was used until 2016/17 (cost in that year was £395)?

a) and c) We acknowledge the administration cost was not updated according to the most recent figure. The updated tariff (QZ14B – 2016/2017) should be £213.00 and reflected in the economic model submitted along this response. The NHS list

price of a 5ml vial is £750 excluding VAT and it is the price applied in the model as stated in the CS.

b) The NHS list price of a 5ml vial is £750 excluding VAT and it is the price applied in the model as stated in the CS. The cost per cycle is calculated based on the license dose (2 mg per kilogram per week) and the average weight of patients per health states (Weight assumption based on MAA patients). The model is programmed around a yearly cycle; therefore 52 weeks is estimated per year. Although the option available in the model to include additional utility for patients have home infusion, this assumption was not included in the based or in any of the scenario analysis (sheet 'Controls', cell E79).

B27. Priority question. Please replace the 2006 values for spinal decompression/lower spine surgery with appropriate spinal reconstructive procedure cost codes from the reference cost schedule 2018-19.

The spinal decompression/lower spine surgery is updated as follows:

Original Model assumptions as Base case		Spinal reconstructive procedure updated as ERG request	
£[redacted]	Assumed same as spinal decompression	£[redacted]	HC60A Very Complex Extradural Spinal Procedures with CC Score 4+

Table 58: B27 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

Total	Incremental	ICER

	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£			£			£
Elosulfase Alfa	£						

B28. Priority question. Please remove the 20% VAT waiver cost from the drug acquisition costs. As outlined in the original ERG report for elosulfase, according to the NICE methods guide, VAT should be excluded from all economic evaluations, therefore there would be no difference between the drug cost between home and hospital care.

The 20% VAT waiver was included in the economic model as scenario analysis (sheet "Scenario Management") attached to the ERG clarification document.

B29. Priority question. The ERG notes that the company used the mean weight of patients per wheelchair state to estimate the cost of elosulfase. However, the weight range in the MAA was quite broad (10 to 68.4kg) and, therefore, the number of vials of elosulfase required will change according to weight categories in the MAA dataset. Therefore, please divide patients into weight categories in the MAA and assess the proportion of patients requiring a different number of vials in order to estimate weighted treatment costs. Further clarification requested by ERG on 08/02/21: Please can the company provide an average weight and number of vials per wheelchair state.

Updated response submitted by Company on 12/02/21:

The average weight and number of vials implemented in the economic model is provided in the table below:

Health State	Average Weight per Patient (Kg)	Vials per week*	Vials per cycle (Year)	Source
Asymptomatic				Same assumption as HST2 (2015)
No wheelchair use				MAA dataset (
Sometimes use wheelchair				MAA dataset ( )
Wheelchair dependent				MAA dataset ( )

*Vials consumption calculation: (Patient Weight * 2 mg dose)/5 mg vial dose). Economic model output is RoundUp to account the excess of dose in the total cost per patient.

As provided in the CS, the average weight of patients treated in the MAA remained stable over time after reaching adult height (Figure below). Younger patients tended to gain weight in line with growth and there was no important weight variation in adult patients.

MAA weight over time by age at treatment initiation

[redacted]

Previous response submitted by Company on 02/02/21: The broad range of weight noted by ERG would not justify a new method of vial consumption in the economic model based on the exercise presented below (Excel shared along with this document.) There is no difference between estimate the average vials consumption based in the average population weight or calculating based on the individual patient weight.

Table 59: Average vial estimate

	Estimate of vials based on the Mean Weight
Average Weight	[redacted]
Average Vial estimate	[redacted]

	Estimate of vials based on the Mean Weight
The sum of vials per each patient	[redacted]
Number of patients	[redacted]
Average Vial estimate	[redacted]

B30. Priority question. Please add the pre-medication drugs as detailed in table 85 of the CS into the economic model.

As agreed in the TC with the ERG on 20 January 2021, a qualitative description of AEs and their magnitude and severity is provided below. Pre-medication drugs described in Table 85 of the CS have already been accounted for in the cost assumption in the model as part of the administration cost, as most patients receive low-cost drugs such as antihistamine and paracetamol medications prior infusion with elosulfase alfa, in line with clinical trial and treatment protocols.

According to the PBRER report for Vimizim submitted to EMA on [redacted] for the reporting period [redacted] global marketed exposure at this time was estimated to [redacted] patients. Specific information about which medicines were used as pre-treatment is not available in this report. Infusion reactions, defined as adverse reactions occurring during the time period between the start of a Vimizim infusion and the end of the day following that infusion, were observed in [redacted]% of subjects across all 6 clinical studies in the clinical development program. Of the infusion reaction events, [redacted]% were reported as serious and [redacted]% as non-serious (see below details on most comment serious and non-serious events). Of the [redacted] confirmed anaphylaxis events, [redacted] of them happened within 1 day of infusion and few of them were treated with epinephrine (see below details on treatment used to treat events).

Infusion reactions:

Cumulatively until [redacted] (PBRER), a total of [redacted] infusion reaction events in [redacted] cases have been reported from spontaneous and serious solicited cases. Of these, a total of [redacted] events in [redacted] cases were reported within 1 day of the administration of the patient's infusion. Of these [redacted] events, [redacted] events have been reported as serious, and [redacted] events have been reported as non-serious. The most common serious events reported within 1 day of the administration of the infusion have been hypersensitivity [redacted], infusion related reaction [redacted], anaphylactic reaction [redacted], bronchospasm [redacted] and urticaria [redacted] The most common non-serious events reported within 24 hours of the administration of the infusion have been rash [redacted], urticaria [redacted] infusion related reaction [redacted] pruritus [redacted] erythema [redacted] and hypersensitivity [redacted]

Anaphylaxis:

A cumulative search using the broad algorithmic anaphylactic reaction SMQ search terms identified [redacted] potential cases of anaphylaxis within the post-marketing setting. All [redacted] cases were individually reviewed, of which [redacted] cases reported anaphylaxis or met the NIAID/FAAN 2006 criteria (Sampson 2006) for anaphylaxis. [redacted] cases occurred within 1 day of infusion. Of these [redacted] cases, [redacted]cases did not report any medications used to treat the event; [redacted] cases reported the anaphylactic or suspected anaphylactic event was treated with epinephrine with or without supportive therapy or other medications; [redacted]cases reported using a combination of antihistamines and steroids; [redacted] cases reported treating the patient with only antihistamines; [redacted] cases reported treating the patient with only steroids; [redacted] case reported steroids and paracetamol; [redacted] cases reported only supportive therapy (i.e., supplemental oxygen and intravenous normal saline) for treatment of the event; [redacted] cases

reported treating the event with paracetamol; and [redacted] case was treated using nasal and inhalant steroids. The remaining [redacted] cases reported using a combination of supportive, antihistamine and steroids to treat the event of suspected anaphylaxis.

B31. Priority question. On page 374 of the CS the company indicates that home infusion is done with or without the supervision of a nurse. Please provide costs and proportions for home infusion supervised by a nurse and home infusion not supervised by a nurse and include the results as a scenario analysis in the model.

We estimate about [redacted]% patients are fully or semi-independent for their infusion and [redacted]% are fully dependent on nurse based on nurse input from RMCH treatment centre.

- Semi-independent patients: drug delivered to patient home, the nurse prepares the infusion, cannulates the patient, sets the infusion running, then leaves; this way they avoid the cost of paying for the nurse to sit around observing the patient during the infusion for 4 hours
- Fully independent patients require no nurse support but would incur a delivery cost for the drug. Independent patients are carefully selected (there are clear exclusion criteria for independence), elosulfase alfa is shipped to the patients' house and the patients or carers / parents take charge. This only take place after an adequate training period with parents, carers or patients that have demonstrated high levels of activation (knowledge and engagement with their disease)

In the base submission the proportion of patients receiving home infusion in the model was set to define the additional utility values for patients receiving the treatment at home (as explained in B26) and not to affect the administration cost.

[redacted]

The administration cost method developed for this scenario analysis is described below:

- The cost for Home infusion is defined according to the patient category and proportion as defined above. The NHSE have negotiated with homecare companies through the national framework (for all enzyme replacement infusions) the cost of £[redacted] per infusion. For the semi-independent patients the cost of four hours of nurse supervision (PSSRU 2019, nurse cost per hour is £40) is deducted from the total £[redacted]. (Sheet 'Costs', cells B100 to B114)

Table 60: Administration cost and proportion of nurse-supervised patients

Semi-independent Patients		Spinal reconstructive procedure updated as ERG request	
Administration cost	Proportion	Administration cost	Proportion
£[redacted]	[redacted]%	£[redacted]	[redacted]%

The results are provided below and available in the economic model submitted along with this document.

Table 61: B31 scenario analysis results

Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

B32. Please conduct a scenario analysis where the proportion of parents or legal guardians caring for children is 70%.

The scenario analysis is provided as request by ERG (results provide below) in the economic model attached to the ERG clarification document (see sheet 'Scenario Management').

A summary of the results is provided below:

Table 62: B32 scenario analysis results

Discounted results

Total	Incremental	ICER

	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life Years	Costs	QALYs	Life Years	
No treatment	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
Elosulfase Alfa	£[redacted]	[redacted]	[redacted]				

Model results

B33. Priority question. In the "results" tab in the model, please include a table with total undiscounted life years gained for each health state of the model, for both treatment arms. Please can the company double check if no errors were made on these calculations as, for example, the undiscounted life years for the no treatment arm, asymptomatic state (0.13) are lower than the corresponding discounted value (0.17).

Updated response by Company (12/02/21):

The inconsistent values are due to an inaccurate summing formula in the 'results' sheet and limited to the asymptomatic health states, which means there is no impact on the overall results. The correction is done in the economic version submitted along with this response.

Previous response submitted 02/02/21 by the Company: A table of total undiscounted life years gained was added in the economic model (sheet "Result") for base case and additional scenarios requested by the ERG in this clarification questions.

B34. Priority question. In the "results" tab in the model, please include a table with the proportion of surgeries estimated per health state, for both treatment arms.

A table of surgical interventions per health state was added in the economic model (sheet "Result") for base case and additional scenarios requested by the ERG in this clarification questions.

B35. Priority question. In the "results" tab in the model, please include a table with the discounted QALY gain and the undiscounted life years gained per surgery for both treatment arms.

A table of utility decrement due to surgery per health state was added in the economic model (sheet "Result") for base case and additional scenarios requested by the ERG in this clarification questions. However, the surgery impact in life years per health state was not programmed across the Markov traces. A table with discounted life years is provided in the 'Results' sheet.

B36. Priority question. In the "results" tab in the model, please include a table with the undiscounted QALY gain for each health state of the model, for both treatment arms. Further clarification requested by ERG on 08/02/21: Similar to the question B33, please can the company double check if no errors were made on these calculations as, for example, the undiscounted QALYs for the no treatment arm, sometimes WC state ([redacted]) are lower than the corresponding discounted value ([redacted]).

Updated response by Company (12/02/21):

The undiscounted QALYs was incorrectly programmed across the treatment arm health states, this was corrected in the model submitted along with this response.

The correction impacted the overall result in additional [redacted] undiscounted QALYs, as table presented below.

Undiscounted QALYs	Base Case (Original Submission)	Base Case (With correction)	Change
No treatment	[redacted]	[redacted]	[redacted]
Elosulfase Alfa	[redacted]	[redacted]	[redacted]

Previous response submitted 02/02/21 by the Company: A table of undiscounted QALY gain per health state was added in the economic model (sheet "Result") for base case and additional scenarios requested by the ERG in this clarification questions.

B37. Priority question. Please provide graphs (traces) with the evolution of the proportion of patients in each health state of the model (per treatment arm, respectively). Further clarification requested by ERG on 08/02/21: Please can the company correct the comparator trace as column AT of tab "Markov_Trace_Soc"

shows several error messages on the distribution of patients across the Markov states adding to 100%.

Updated response by Company (12/02/21):

Although some errors were identified in the patient distribution across the columns W to BT, the sum of all health states are still resulting 1, as it is presented in the column U. Therefore, the minor variations in the individual health states are not affecting the final result.

The company acknowledges in cycles 52 and 58-62 of the overall patient distribution (Column U) is not summing 1; however, the difference is minimal (15th decimal place) and not affecting the results of the economic model.

Previous response submitted 02/02/21 by the Company: The traces with the evolution of patients through the health states were added in the economic model (sheet “Markov Trace”) for base case and additional scenarios requested by the ERG in this clarification questions.

Figure 8: evolution of the proportion of patients in each health state of the mode per treatment arm

[redacted]

B38. Priority question. Please provide graphs (traces) for patients’ survival for both treatment arms.

The survival curves were added in the economic model (sheet “Survival_Curve”) for base case and all the additional scenarios requested by the ERG in this clarification questions.

Figure 9: Base case scenario survival in each treatment arm

[redacted]

Section C: Textual clarification and additional points

C1. Please can the company provide details of MOR-003, assuming there was a study planned to be named MOR-003.

No MOR-003 study was planned.

C2. The ERG found several discrepancies between the model inputs reported in the CS and used in the economic model. Can the company please clarify which of the following sources are correct:

a) Table 87 in the CS (for year 1 and subsequent years in both the placebo and the elosulfase arms) does not match the values reported in the spreadsheet "Efficacy" C73:J79; and C84:J90; C96:J102; C106:J112; C116:J122.
b) Table 80 in the CS reports that asymptomatic patients had a baseline FVC of 100% while the model reports 80% (tab "efficacy", cell E142).
c) Table 81 in the CS and the table in tab "efficacy", E168:G171).
d) Table 84 gives the probability of cataract surgery succeeding as 78% with a 10% of paraplegia and 12% risk of death, where in the model this is 97.9%, 0% and 2.1%. (Surgery!D42:F42)
e) Table 77 - change in wheelchair use. The values for 'Some use WC' for the MAA dataset add up to >100%.
f) The surgical rates reported on page 357 of the CS as being the final proportions do not match what is used in the model or in table 83.

a) The figures were inaccurately reported in the CS. Please find below the tables with values according to the economic model.

Table 63: Tables with corrected values in the model

C73:J79:

Natural History Patients (1st cycle only)	Asympto-matic	No a wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End stage	Death from End Stage Only
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sometimes use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Predeath	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C84:J90:

Natural History Patients (subsequent cycles)	Asympto-matic	No a wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sometimes use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predeath	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C96:J102:

Elosulfase Alfa treated patients (1st cycle only)	Asympto-matic	No wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sometimes use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predeath	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C106:J112:

Elosulfase Alfa treated patients (Long-term stabiliser 2nd cycle onwards)	Asympto-matic	No wheel-chair use	Some-times use wheel-chair	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sometimes use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predeath	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C116:J122

Elosulfase Alfa treated patients	Asympto-matic	No wheel-chair use	Some-times use	Wheel-chair depen-dent	Paraplegic	End Stage	Death from End Stage Only

(mild decliner 2nd cycle onwards)			wheel-chair				
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wheelchair us	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sometimes use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predeath	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) The figures were inaccurately reported in the CS. The correct figure is [redacted]% as reported in the economic model. Please refer to the question B12 for additional context on this functionality.

c) The Table 81 were inaccurately reported in the CS. Find below the tables with values according to the economic model:

	FVC%		Relative Risk Mortality
	Treated	% Decrement	
Asymptomatic	[redacted]%	[redacted]%	[redacted]
No wheelchair use	[redacted]%	[redacted]%	[redacted]
Sometimes use wheelchair	[redacted]%	[redacted]%	[redacted]
Wheelchair dependent	[redacted]%	[redacted]%	[redacted]

d) The Table 84 were inaccurately reported in the CS. Find below the tables with values according to the economic model

Surgery	Successful	Paraplegic	Death
Cataract surgery	[redacted]%	[redacted]%	[redacted]%

e) The Table 77 were inaccurately reported in the CS. Find below the tables with values according to the economic model.

MAA dataset, November 2019

Last Follow-up	Baseline	No use WC	Some use WC	WC dependent
	No use WC	[redacted]%	[redacted]%	[redacted]%
	Some use WC	[redacted]%	[redacted]%	[redacted]%
	WC dependent	[redacted]%	[redacted]%	[redacted]%
	MOR-001 (based on 2-year data)			
2-years assessment	Baseline	No WC	Occ. WC	Always WC
	No use WC	79%	3%	0%
	Some use WC	21%	72%	17%
	WC dependent	0%	24%	83%

f) The surgical rates reported in page 357 were estimated by clinical experts in the UK via a Modified Delphi-Panel. However, the surgical rates for base case in the model were adjusted based on literature. A scenario analysis using ERG request surgical values is presented in B13.

C3. In the Main Source Update sheet, most of the cells in column E are linking to a sheet with the path: 'https://bmrn-my.sharepoint.com/personal/an902941_bmrn_com/Documents/Vimizim/Vimizim NICE HST submission (Dec 2020)/9. 2020 updated health economic models/Final Version for Submission/[MAA_database_NICE_C-E_Model_v05.xlsm. Please update this reference.

The reference was updated in the economic model.

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Patient organisation submission

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2) [ID1643]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Rare Disease Research Partners (RDRP)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	MPS Commercial is a Private Limited Company Registered No. 08621283. MPS Commercial trades as Rare Disease Research Partners and is a wholly owned, not for profit subsidiary of the Society for Mucopolysaccharide Diseases (the MPS Society), Registered Charity in England and Wales No. 1143472. Rare Disease Research Partners' social objectives are to reinvest any profits to support the MPS Society mission of transforming lives through specialist knowledge, support, advocacy and research. RDRP provides professional services to the pharmaceutical industry.
4b. Has the organisation received any funding from the manufacturer(s)	RDRP has received fees for professional services provided to BioMarin.

of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from,	None

the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	RDRP has been responsible for collecting the patient reported outcome (PRO) data throughout the elosulfase alfa Managed Access Agreement (MAA). While interviewing patients to collect this data, we have conducted our own independent research to gather information on treatment effects that may not be captured by the PRO tools used in the MAA (1). In addition to this, we conducted a patient and caregiver survey in collaboration with the MPS Society UK, to obtain more detailed testimony on the effects of treatment in January 2020 (2). 1. Rare Disease Research Partners. Patient and caregiver experience of treatment with elosulfase alfa under the Managed Access Agreement. Unpublished report. March 2020 2. Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. March 2020
Living with the condition	
6. What is it like to live with the condition? Consider • the experience of living	Mucopolysaccharidosis type IVA (MPS IVA) is a heterogeneous and progressive disorder. Patients typically show widespread skeletal and joint abnormalities, including dwarfism with short trunk and neck, genu valgum, hip dysplasia, joint hypermobility, spinal abnormalities and pectus carinatum. These skeletal abnormalities generally result in impaired endurance, walking ability and gait (1). Cardiopulmonary disease (including tracheal stenosis/malacia and dyspnoea) and spinal cord compression may further reduce endurance and/or mobility (1). Other manifestations include corneal clouding and hearing loss (2). The clinical manifestations of the disease and resulting impaired mobility can reduce the patient's ability to perform activities of daily living (ADL), such as attendance at school or work and social activities. The patient's quality of life (QoL) can be further compromised by frequent infections, impaired vision or hearing, frequent surgeries, (joint) pain and fatigue (1).

with the condition and the impact on daily life. • explaining anything that has changed since during the period of the managed access agreement (MAA) (include date span).	Patients retain normal intelligence. Many people with MPS IVA continue into further education. In a UK study, 47% of patients entering further education studied for honours or higher degrees (3). Adult patients are often employed and functioning in society, as long as physically capable. Reduced physical functioning/mobility may therefore not only impact on the patient's QoL but may also require a significant amount of care and increase the burden on society as a whole (1). The progressive nature of untreated MPS IVA causes a gradual reduction in the patient's functional capacity, mobility, and autonomy. This places a huge burden on the caregivers of individuals with this disease and considerably affects their QoL, health, family and social life, employment, and finances (4). Respiratory impairment and spinal cord instability are the main cause of morbidity and mortality (2). The life expectancy of patients varies considerably, with patients survival varying between the second decade of life and near-normal life expectancy (1). In our experience of talking to patients and their parents or cargegivers regularly over the last four years, fatigue has a major impact on QoL. Patients often tell us that before treatment with elosulfase alfa, they would need to plan their day to avoid becoming exhausted and to manage their pain. Untreated children would come home from school too tired to join in after school activities and untreated adults would need to spend time recovering in the evenings and at weekends from their working week. 1. Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. Orphanet journal of rare diseases. 2014;9:32-. 2. Akyol1 MU, TDA, HA, JA, KB, KIB, et al. Recommendations for the management of MPS IVA: systematic evidence- and consensus-based guidance. Orphanet Journal of Rare Diseases. 2019;14:137. 3. Thomas S MA. The educational journey of individuals with MPS IVA Morquio disease. International MPS Symposium; Bonn, Germany. Poster presentation2016.

• what carers experience when caring for someone with the condition?	4. Christian J. Hendriksz M, CL, MC, MD3, , Sema Kalkan Ucar M, MJ, PhD4, et al. The Burden Endured by Caregivers of Patients With Morquio A Syndrome: Results From an International Patient-Reported Outcomes Survey. Journal of Inborn Errors of Metabolism & Screening. 2014.
Treatments of the condition in the NHS	
7. How has this treatment fitted in with the other treatments and care for the condition available on the NHS?	Elosulfase alfa fits and is an essential addition to the current supportive management and standard of care. The only disease modifying treatment for MPS IVA in England is elosulfase alfa, currently only available under the MAA. The majority of eligible patients have chosen to accept treatment with elosulfase alfa by signing up to the Managed Access Patient Agreement. As of 6th February 2020 at total of 72 patients had joined the MAA, 10 were ineligible for treatment and 17 had declined treatment (Table 1).

Table 1. England MPS IVA patient totals

Centre	Number patients joined MAA at this centre	Number ineligible for MAA	Number declined MAA	Number currently on treatment	Number stopped treatment at this centre
Birmingham Children's	11	2	5	10	0
Great Ormond Street	18	1	2	14	1
University College London	10	1	3	10	3
QE Birmingham	4	1	2	5	0
Royal Free	4	0	2	3	1
Salford Royal	8	3	3	11	1
St Mary's Manchester	17	2	0	9	4
TOTAL	**72**	**10**	**17**	**62**	**10**

8. What place do you think this technology has in future treatment and care?

The effectiveness of treatment has been demonstrated during the MAA. Given the success of the MAA, with most patients continuing to meet the criteria for continuation of therapy, we expect that elosulfase alfa will continue to be available to patients in England.

Recent international consensus guidelines on management of MPS IVA includes the use of elosulfase alfa as standard (1).

Without elosulfase alfa, no disease modifying treatment will be available on the NHS and patients will receive supportive care only. We believe that given the effectiveness shown during the MAA and the reduction in the uncertainty of long-term effect, this would be an unacceptable position for patients.

1. Akyol et al. Orphanet J Rare Dis 2019;14:137

Advantages of the technology (including those experienced through the managed access agreement [MAA])

9. What do patients or carers think are the advantages of the technology?

Patients think that elosulfase alfa is a life-transforming treatment that gives them significant improvements in their quality of life.

We have collected reports of patient and caregiver experience throughout the MAA. The results of this have been analysed and reported in an attachment to this submission (1). In this study, many benefits to patients' quality of life were reported.

In conjunction with the MPS Society, we have also conducted a patient and caregiver survey to answer this question, see attachment to this submission (2).

Below is just one example (that is reflective of the view of many patients) of how treatment with elosulfase alfa has changed a patient's

	life from the survey: *'The sustained benefit of increased endurance given by Vimizim is life-changing. I used to be a child without treatment, always forced to sit out of social events (such as birthday parties, play dates etc.) due to a lack of endurance and the fear of being exhausted, and now I am able to work full-time, getting involved in social events, both professionally and with friends and family. This is normality for some, but it was a pipe dream for me before Vimizim.'* 1. Rare Disease Research Partners. Patient and caregiver experience of treatment with elosulfase alfa under the Managed Access Agreement. Unpublished report. March 2020 2. Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. March 2020
Disadvantages of the technology (including those experienced through the managed access agreement [MAA])	
10. What do patients or carers think are the disadvantages of the technology?	The majority of patients think that the burden of the administration of elosulfase alfa is outweighed by the broad benefits In conjunction with the MPS Society, we have conducted a patient and caregiver survey to answer this question, see attachment to this submission (1). 1. Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. March 2020
What was measured during the managed access agreement [MAA]	
11. Thinking about the things that got measured during the period of the managed access	Our views of the measures used in the MAA are: o 6-minute walk test or 25ft ambulation for endurance – for patients' mobility and endurance are important outcomes but these are very poor measures o FEV1 and FVC for respiratory function – from a patient point of view we have no view on this measure o Ejection fraction for cardiac function – from a patient point of view we have no view on this measure o Urine keratan sulfate – from a patient point of view we have no view on this measure o Patient reported outcomes MPS-HAQ, EQ-5D-5L, Beck Depression Inventory and Brief Pain Inventory/Adolescent Paediatric

agreement (MAA), do you think that all the things that are important were measured? Please list what they were and why they were important (or unimportant).	Pain Tool for quality of life – These are important outcomes for patients, however the Beck depression inventory is a very poor tool for measuring outcomes as it is not a balanced measure of mental health or mood. It is only a screening tool for depression (please see next section). These have provided a framework for assessing patients equitably across treatment centres and a method to determine response to treatment and whether or not the patient should remain on treatment. The measures have provided a means to track patients' progress in a real world setting and resulted in a rich data set to extend understanding of treatment effects outside of a clinical trial setting.
12. Were there things that were not measured but important? If there were, please list what they were and	The choice of quality of life measures can be difficult in rare disease, with few specific measures available. Patients and caregivers often mention treatment effects that may fall outside of the standard PRO measures used in the MAA. For example, the Beck Depression Inventory can be used to screen for patients that may be suffering with depression, and record any improvement seen. It has identified patients with depression pre-treatment who have improved after starting elosulfase alfa. It is however, less able to detect changes in patients who may not be depressed before they start treatment, but nevertheless feel psychologically better on treatment. This can be illustrated by looking at the question on sleep from the Beck Depression Inventory. The answer options are: o I can sleep as well as usual o I don't sleep as well as I used to o I wake up 1-2 hours earlier than usual and find it hard to get back to sleep o I wake up several hours earlier than I used to and cannot get back to sleep Patients often mention that they sleep better since starting treatment, yet there is no option in the PRO measure to record 'I sleep better

why they are important.	than usual.' The treatment benefit that most patients report is endurance in terms of having more energy or being able to do more. This and other effects such as reduced fatigue are not adequately captured by the PROs. Patients and their healthcare professionals have also noted that those treated with elosulfase alfa have less illnesses and infections requiring antibiotic use (1). Healthcare professionals consider that the availability of elosulfase alfa has increased their expectations for their MPS IVA patients. They now expect them to be well, live longer and be candidates for surgeries that would not have been considered for these patients previously (1). For these reasons we have undertaken a number of activities to describe these additional effects and the results are attached to this submission (1-3). 1. Rare Disease Research Partners and MPS Society. Observations of elosulfase alfa treatment benefits in specialist Lysosomal Storage Disorder centres in England. Unpublished report. January 2020. 2. Rare Disease Research Partners. Patient and caregiver experience of treatment with elosulfase alfa under the Managed Access Agreement. Unpublished report. March 2020 3. Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. March 2020
Patient population (including experience during the managed access agreement [MAA])	
13. Are there any groups of patients who might benefit more or less from the technology	From our data all patients benefited from elosulfase alfa.

than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that that should be taken into account when considering this condition and the technology?	No comment
Other issues	
15. Are there any other issues that you would like	The communication with the patient community has not been clear or forthcoming. The process for evaluation has not been clear, it appears to have been changed and continues to change. Patients and caregivers are experiencing considerable anxiety around the uncertainty of the process for considering the long-term use of elosulfase alfa. They remain worried that the significant benefits they experience will not be reflected in the outcome of the process.

the committee to consider?	
16. Are you aware of any patients who declined elosulfase alfa through the managed access agreement? If so, what are the reasons for this?	We are aware of a total of 17 patients who declined treatment on the MAA. We do not have any information about their reasons. Nine patients have chosen to leave the MAA (patient/family decision n=3, extended travel n=1, misdiagnosis n=1, line or cannulation issues n=3, left the country n=1).

Key messages

17. In up to 5 bullet points, please summarise the key messages of your submission:

- The majority of patients gain both clinical and quality of life benefits from treatment with elosulfase alfa
- Patients quality of life is significant and sustainably enhanced by treatment
- Treatment benefit has been demonstrated in patients starting treatment at all ages

- Elosulfase alfa has become the international standard of care
- Elosulfase alfa has an essential place in the future management of patients with MPS IVA

➢ *Additional guidance for submissions following a managed access period:*

Please include a brief summary of the key points in the submission addressing:

- *Any new evidence since the original submission that impacts:*
    - *Nature of the condition*
    - *Impact of the new technology*
    - *Impact of the technology beyond direct health benefits.*
- *Results from the managed access data collection*
- *Outcomes collected through the managed access period that address the committee's key uncertainties from the original evaluation.*

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Patient organisation submission

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2) [ID1643]

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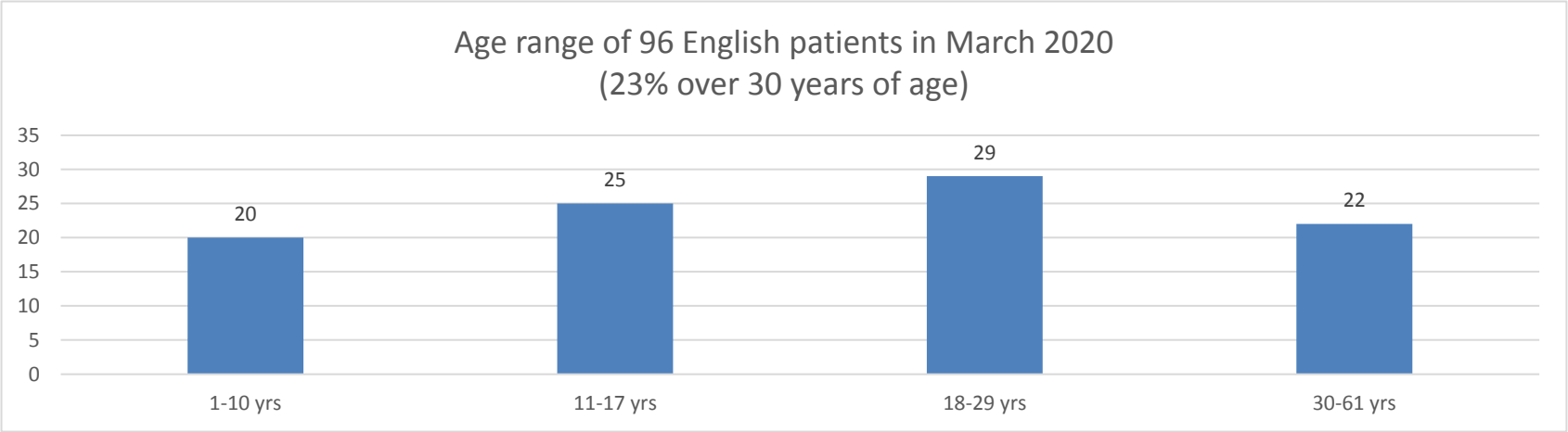
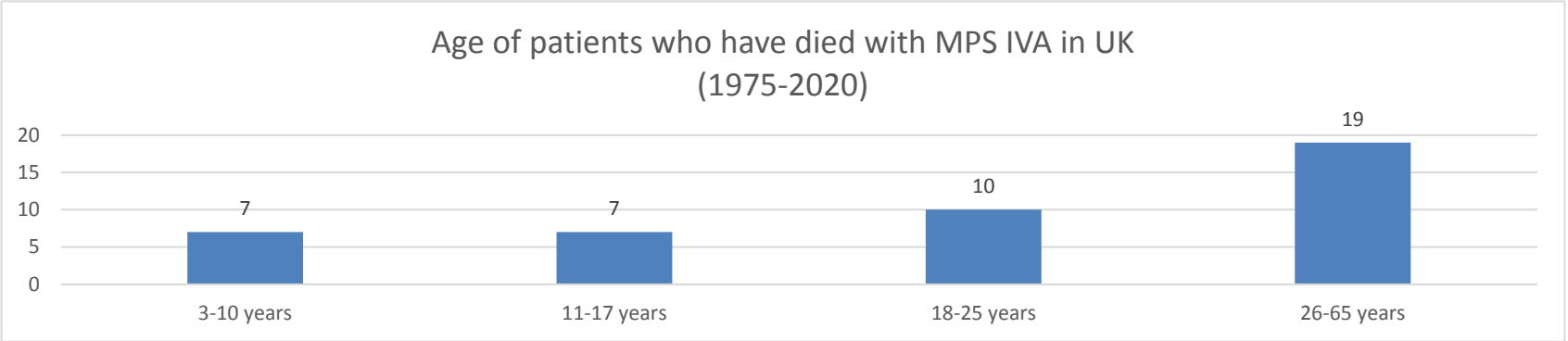
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The MPS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MPS Society is the only organisation in the UK that provides support to patients diagnosed with one of 25 MPS or related lysosomal disorder. The organisation supports over 1,500 children, adults and families. The MPS Society was established in 1982, with the aim of providing support, information, and advice to affected individuals and families. We offer specialist support, information and advocacy, working in partnership with individuals, families, health, statutory services and other relevant professionals, ensuring that the individual and their needs always remains our main priority and that they have access to the specialist care, services and treatment that they need. The MPS Society does not receive any statutory funding in England, therefore the MPS Society relies upon a rolling programme of grant applications to Trusts and Foundations, together with monies raised by members and the public through fundraising. The MPS Society receive grants from pharmaceutical companies for the different activities it provides.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	The MPS Society has received funding in the last 12 months from BioMarin for its activities for 2020. This amounts to £56,000 and is for the following activities: • Advocacy & Support services • Information, communications & support relating to COVID-19 pandemic • Research project • Expert consensus meeting on COVID-19

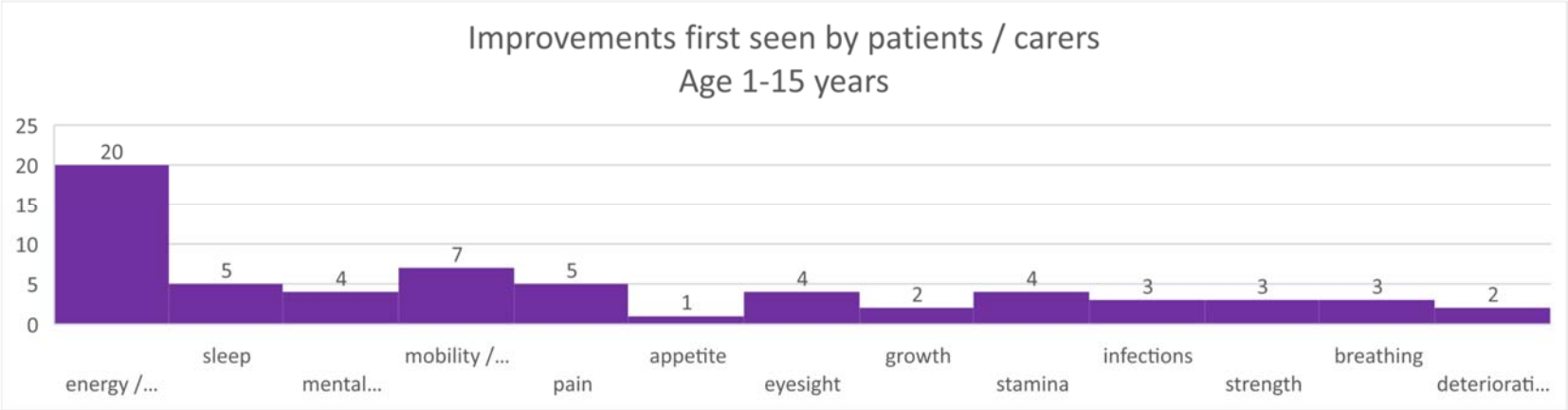
If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Non
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patient self-reporting Clinical roundtable discussion (1) Patient reported outcomes during the MAA (RDRP) (2) Patient / caregiver experience of treatment – UK survey (3) / (5)[redacted] (1) Rare Disease Research Partners and MPS Society. Observations of elosulfase alfa treatment benefits in specialist lysosomal storage disorder centres in England. Unpublished report. January 2020 (2) Rare Disease Research Partners. Patient and caregiver experience of treatment with elosulfase alfa under the managed access agreement. Unpublished report. March 2020. (3) Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. March 2020. (4) Thomas S MA. The educational journey of individuals with MPS IVA Morquio disease. International MPS Symposium; Bonn Germany. Poster presentation 2016. (5) [redacted]

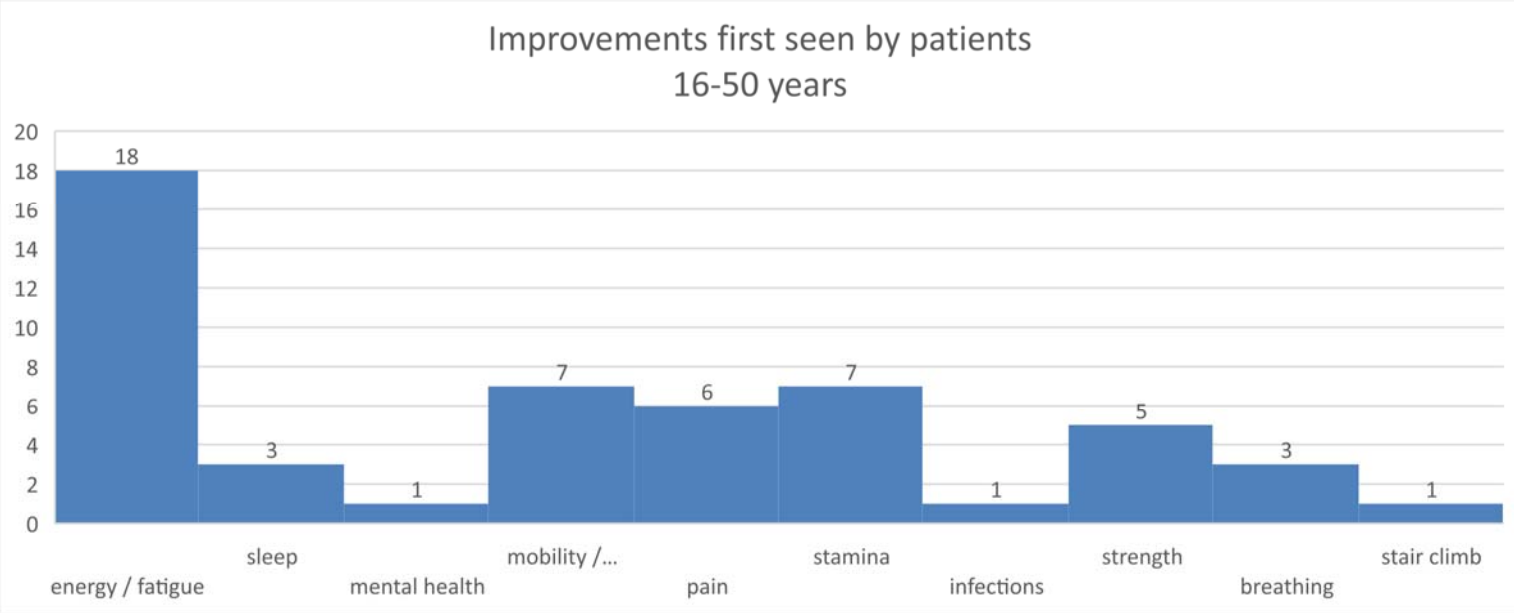
Living with the condition	
6. What is it like to live with the condition? Consider • the experience of living with the condition and the impact on daily life. • explaining anything that has changed since during the period of the managed access agreement (MAA) (include date span).	MPS IV, Morquio disease is a rare autosomal recessive condition. We estimate that approximately 3-4 patients with be diagnosed with this condition per year. Data reviewed in March 2020 confirmed that the MPS Society was aware of 120 patients across the UK, with 96 patients living in England.  Morquio patients typically are usual weight and length at birth. By the age of 18 months, there is usually a noticeable decline in growth and this usually stops by the age of 8 years. Average height is between 90cm and 150cms. Difficulties seen are; cervical spine instability; upper airway difficulties, repeated infections, skeletal dysplasia, hip dysplasia, fatigue due to pain and respiratory issues, cardiopulmonary disease (including tracheal stenosis) joint laxity, knock knees, corneal clouding and hearing loss. Patients are not normally neurocognitive impaired and are high achievers academically. A study carried out in 2014 showed that 47 % of patients had gone on to further education and achieved a degree or higher (4) (The educational journey. Poster presented at Bonn 2016)

• what carers experience when caring for someone with the condition?	Due to the positive effects of treatment, many patients have reported changes in multiple areas including; energy, mobility strength and pain that have had a positive effect on their mental health and ability to do more and contribute to society since being on treatment. Before treatment, many patients had poor mental health, were having to miss large periods of school and work due to pain and were worried for their future and the impact on family and peers. From the 2020 Patient caregiver experience of treatment - UK survey (4); 19.51% of adult patients were in active employment with many reporting that their capacity to work had increased while on treatment. Their ability to do other things outside of work and at weekends had also increased. One patient has given a compelling account via video presentation of her journey to diagnosis, access to treatment and the impact this has made to her life (5) In reviewing the "Mortality in Patients with Morquio syndrome A" paper (Lavery et al 2014), which was a review of death certificates from 1975 to 2010. The mean age of death was 25 years. The expectation of treatment from this paper was the hope that "novel disease-specific treatments such as enzyme replacement therapy would help to extend the lifespan of patients with Morquio further still" (Lavery et al 2014). In reviewing, the MPS Society's Morquio database of known deaths from 1975 - 2020 the chart below shows that 43% of patients who died were over 25 years. In the period of (2014-2020), 5 patients over the age of 25 years have died. Three of those were over the age of 40 years. 

	In addition to the clinical and quality of life measures collected throughout the duration of the MAA, patient and carers have reported a number of positive impacts on daily living and their Q of L. Please see patient and caregiver experience of treatment – UK survey 2020. Some key carer comments are below; *"I stopped working when my child got on the drugs trial. I now work part time in another job and work from home on her infusion day".* *"As being on treatment has made my child healthier and have more energy and stamina then knowing that they are on the whole able to be in school full time has made it possible for me to plan when I am able to work".* *"Obviously being part of the clinical trial was a big commitment and impacted on my ability to work, but once infusions switched to taking place in school then I was able to return to part time work".*

Treatments of the condition in the NHS	
7. How has this treatment fitted in with the other treatments and care for the condition available on the NHS?	There are no equivalent treatments for this condition. All eligible patients were offered treatment, with 75 patients being enrolled on the MAA. 12 patients have ceased treatment. 2 patients died and 10 patients had to stop treatment for the reasons listed below. The current number of treated patients is 63. 25 patients did not enrolled on the MAA with 7 being ineligible and 18 declining treatment. Reasons for stopping included • Patient / family decision to withdraw • Extended travel / leaving the country • Line and port issues / cannulation issues • Significant reactions, decline in MAA parameters • Treatment unsuitable – full diagnostics indicated MPS IVB • Failed MAA criteria The treatment does not have an effect on the bones and joints so many of the surgeries required in this cohort of patient's remains. Clinicians have reported that patients are now in better condition and expected to live longer. Clinicians are now looking at major surgeries such as tracheal reconstruction, which would not have been considered, 10 -15 years ago. (2020.Observations of elosulfase alfa treatment, benefits in specialist lysosomal storage disorder centres in England) (1) Clinicians are now expecting patients to go on to further education and work and are engaging in these discussions with patients. (1)

8. What place do you think this technology has in future treatment and care?	This treatment should continue to be funded and offered to eligible patients as it has clearly shown a treatment effect, patients are meeting the clinical criteria and reporting good outcomes, sustainability and improvements in everyday life with an increase in societal participation. The effectiveness of the treatment remains with only one patient out of 75 not meeting the response criteria. The remaining patients who came off treatment were for other reasons as listed above. In the recently published international consensus guidelines for MPS IV, elosulfase alfa (Akyol et al. 2019; Recommendations for the management of MPS IVA: systematic evidence- and consensus-based guidance) is included as the treatment choice for this condition.
Advantages of the technology (including those experienced through the managed access agreement [MAA])	
9. What do patients or carers think are the advantages of the technology?	Advantages have been collected through patient carers reports throughout the MAA; patient carer experience of treatment survey and clinical views. Please see separate reports for full details (2) (3) (5) From the patient carer experience of treatment survey 2020 (3) The below improvements were seen within a few weeks / months of treatment. 



Clinicians reported similar themes such as; patients have more energy resilience, patients sleep better, patients have less respiratory infections, patients can become more independent, expectations for patients have increased (1)
From the anecdotal reports collected over 3 years the most common reported improvements were ; growth and development, mobility, wellbeing, pain immunity and fatigue. (2)

Many adult patients reported that they had the ability to do more, required less breaks, if have a busy day they did not need to rest the next day. Many adults could work during the day and socialise in the evening, which was not possible before treatment.

Parent / carers reported that children had more energy, were able to participate in more physical activities and for longer periods of time. Patients were able to do more without tiring and needing to use a wheelchair. Movement was freer less restricted.
Improvements in height were documented with reports of; average height increases of 2-6cm's. (3)
There was a positive impact on mental health and psychological wellbeing of both patients and carers with reports of having a more positive outlook, greater independence, engaging in life and seeing a future. (3)

	Patients reported that the benefits of treatment were sustained over the course of their treatment even in those who had been on treatment for over 10 years (3) Independence had improved across all ages; more noticeably in the 15-19 years who were able to undertake things such as household chores, travelling independently, driving, preparing a meal. For adults this meant that they could go out more, socialise and travel independently. (3) Below are some patient / carer statements taken from the patient caregiver experience of treatment – UK survey 2020. Please see full document for more patient / carer testimonies (3) [redacted](5) Parent / carers 1-5 years *" She could not walk more than 2 minutes in one occasion and cried with pain and fatigue prior to treatment; after treatment she started to walk and move around without complaint about her pain (she can play and study whole day without showing fatigue)"* *"Another significant change is her strength of big muscle movement such as jumping, skipping, climbing which she could not do before"* Parent / carer 6-10 years *"treatment has definitely given her a new lease of life"* Individual / parent carer 11 – 15 years *"I was wheelchair dependent and struggled to weight bare before treatment but between 4-6 weeks after starting treatment I was able to mobilise myself and carry out any activity I needed or wanted to"* *"I first noticed that my eyesight improved. Sight was brighter sharper, more vibrant".* *"Due to all the pain and invalidity I was mentally in a very low place, receiving the treatment and reducing my pain, increasing stamina and energy, and my sight, aided in increasing my positivity and my mental health"* Individual / parent /carer 16-20 years *"I experienced noticeable drastic physical improvements within 5 weeks of starting treatment"*

	"I also noticed less fatigue. I didn't feel debilitated at the end of the day, which was an everyday occurrence before starting treatment" Individual / parent / carer 21 – 40 years *"I have more energy during the day and do not have to go back to bed as often"* *"When I started I noticed improvement straight away, I had two crutches and leg braces and my health was going downhill fast and probably would not be here if it was not for the Vimizim. Everything has improved, no longer need crutches, fitness, strength quality of life has improved, not been for any operations since on the drug or treatment injections since, my health is in the best condition considering my age".* Individual 41 – 50 years *"My mobility improved - I was able to walk without holding on to things for support. My walking improved by 50% after 6 months. The reduced laxity was coupled with the strengthening of my hands, arms and upper core. I was able to climb stairs easier as my arms had the strength to pull my body up using the handrails. I could open the front door into our building, which previously was too heavy for me and needed to rely on others to open. I could open jars, which previously, even if not tight still posed difficulties."*
Disadvantages of the technology (including those experienced through the managed access agreement [MAA])	
10. What do patients or carers think are the disadvantages of the technology?	Disadvantages documented through the patient caregiver experience of treatment survey 2020 were (3) (5); Time it takes to have the treatment; not being able to go on extended holiday; veins failing and issues with cannulation; psychological impact of having infusions /different from peers; home care errors. However for many the advantages outweigh the disadvantages One patients commented on the fact that their back pain had increased a little but this was down to the fact that they were more active and doing more. We are aware of other patients outside of England who have had similar experiences in which they have more energy and are able to do more but this has had a negative impact on pain and their joints, which are unable to support this new lease of energy. Three patient / carers who had stopped treatment reported the following reasons. • Port-a-cath was removed due to infection. Child did not want another one. Decided to discontinue due to impact of long infusions on individual and education • Did not feel benefit they wished for

- Anaphylactic reaction

The impact of stopping treatment meant that;

- Deteriorated physically and is not very mobile
- Remained the same
- Not as strong. Condition worsened and had a negative impact on their quality of life

Recent feedback from patients who had a break from treatment during the first lockdown due to the Covid-19 pandemic (March – July 2020) described an increase in symptoms which included tiredness, fatigue, increased pain, breathing issues, joint pain, raised heart rate, sleeping problems, distress and a decline in mental health. These subsided when treatment resumed.

Patient and caregivers have made a number of comments in relation to their experience of the MAA. Please see the MPS IVA patient and care giver experience of treatment survey 2020 for full details (3). Below are some excerpts from the report.

"The MAA has been interesting. Whilst on one hand it has granted access to this vital drug, and for that we are forever grateful, it does have some shortcomings. Psychologically the message that if you can't walk as far means the treatment isn't working is somewhat over-simplified and worrying for all involved. This is a pressure that a child, or anyone for that matter should not have to endure. The threat of treatment being taken away is damaging for all involved. Life is like a roller coaster. Morquio brings enough challenges for all of us without this as well. I worry about the long term psychological impacts this will have on our brave children who have to put up with so much"

"Vimizim is not a pill. It is spending four hours a week hooked up to a drip. For many it is dealing with allergic reactions, tolerating needles, impinging on leisure time. It is stressful. Genuinely parents would not put their children through this if they did not see the benefits"

"*Lastly Morquio is a progressive condition which worsens as patients get older. The MAA does not take account of this. Measures feasibly could worsen over a decade, and still be far better than they would have been without treatment. This aspect of the MAA is unfair and discriminatory. Taken to its logical extreme it's like expecting a 60 year old to walk as fast as they did when they were 17. And that's without them having a degenerative disease"*

"For the most part I think the MAA has worked well for us, but I don't think the baseline tests are "fair". This is a degenerative condition. Comparing my child's current results with when they were a five year old seems like setting them up to fail. All children change a lot between five and fifteen"

	"I have found the MAA to be an incredibly stressful experience, BUT I will do whatever is needed, anything NICE need me to do in order to keep receiving the drug that was quite literally changed my life, and is giving me a quality of life that I never dreamed possible. I do not want to go back to a life dependent on wheelchairs, stair lifts, and somebody doing my personal care".
What was measured during the managed access agreement [MAA]	
11. Thinking about the things that got measured during the period of the managed access agreement (MAA), do you think that all the things that are important were measured? Please list what they were and why they were important (or unimportant).	The measures used in the MAA were to address the uncertainties that the committee had around the long-term efficacy of treatment within this patient population. They provided a framework for assessing patients based on the tools and measures available at the time, compared to the data collected during the original clinical trial. It gave clear start stops protocols as well as ongoing assessment measures to ensure patients ongoing eligibility. Quality of Life measures helped to capture and interpret the clinical data. The measures have given complete data sets and real world evidence to help answer the committees uncertainties and to help understand the longer-term effects of treatment. Patients felt that the MAA did not take into account the progressive nature of the condition. Please see Patient and caregiver experience of treatment survey 2020 (3) for further details.
12. Were there things that were not measured but important?	From the patient reported outcomes, there were areas of improvement that were not captured during the MAA for example; (1) (2) (3) • Improved energy and fatigue • Improved sleep • Improvements on corneal clouding • Less infections resulting in a reduction in the use of antibiotics. (Please see question 9 for full list of improvements).

If there were, please list what they were and why they are important.	However, we appreciate that choosing appropriate quality of life measures can be challenging in rare diseases, as there are not many validated tools to use. That is why it was important to collect Patient Reported Outcomes, alongside the MAA data to capture self-reported treatment effects and ongoing benefits.
Patient population (including experience during the managed access agreement [MAA])	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All patients currently being treated through the MAA have met the entry criteria and have met all the assessment parameters required and have reported benefits both clinically and socially. This includes a small population of patients who have a severe phenotype. A number of our adult patients have reported significant benefits from the treatment even when treatment commenced late in life. All patients have reported sustained benefits of treatment including those who have been in receipt of treatment for over 5 years. This includes; stabilisation, improved energy, stamina, improved eye sight, improved breathing, less infections, being well enough for surgery (3) Patient / carer reports *"It feels like i have been given a second chance. I see life now as an opportunity to find meaning and enjoyment, where before i was in dread and constant pain. I now feel like, with my medication i can achieve the things i came to realise i would miss out on as my health started to deteriorate before i began to receive Vimizim."* *"Over the course of my adult life, even with as much positivity as i could muster, there were certain setbacks i have encountered that could have been avoided had i been well enough to do so. I now feel optimistic that the goals of which i have had no choice but to compromise on now seem completely manageable with no pain and increased mobility".* *"It's not easy giving up a day every week for treatment, but the benefits by far outweigh the challenges of weekly infusions. I wouldn't have persisted if it hadn't made such a huge difference to my well being and quality of life".* *"The benefits are not only physical. I have a more positive outlook on life as i'm enjoying life more, and have more confidence in myself and what I am capable of doing".*

	"Morquio is a progressive disease and without treatment, patients can only deteriorate, not improve. This makes the improvements experienced as a result of Vimizim more significant. It made me realise how much i was putting up with regarding fatigue and pain, because it was all I'd ever known. I can't imagine a future without Vimizim" *"Vimizim has given my daughter the prospect of a near normal life. I never imagined she would go to University and be so independent. She drives her own car, enjoys a good social life, and is determined to be happy and as mobile as possible. Vimizim has played a crucial role in her life"*
Equality	
14. Are there any potential equality issues that that should be taken into account when considering this condition and the technology?	**No comment**
Other issues	
15. Are there any other issues that you would like the committee to consider?	None

16. Are you aware of any patients who declined elosulfase alfa through the managed access agreement? If so, what are the reasons for this?	We are aware of 18 patients who declined treatment on the MAA. Unfortunately, not many of these patients have commented on their reason why. From the small number of known reasons the below were documented • I was not able to do my job and travel as I wanted to • I would not be able to tolerate having to be cannulated on a weekly basis

Key messages

17. In up to 5 bullet points, please summarise the key messages of your submission:

- Well tolerated and wanted. Compliance has been exceptional for this group of patients
- Treatment benefits have been seen in all ages of patients
- Outcomes have benefited patients and carers greatly
- Patients are contributing to society more
- Surgeries are being considered that were not previously thought viable

➢ *Additional guidance for submissions following a managed access period:*

Please include a brief summary of the key points in the submission addressing:

- *Any new evidence since the original submission that impacts:*
  - *Nature of the condition*

- *Impact of the new technology*
- *Impact of the technology beyond direct health benefits.*

- *Results from the managed access data collection*
- *Outcomes collected through the managed access period that address the committee's key uncertainties from the original evaluation.*

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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OBSERVATIONS OF ELOSULFASE ALFA TREATMENT BENEFITS IN SPECIALIST LYSOSOMAL STORAGE DISORDER CENTRES IN ENGLAND

RESULTS OF A ROUNDTABLE DISCUSSION WITH METABOLIC CONSULTANTS AND METABOLIC NURSE SPECIALISTS

Rare Disease Research Partners

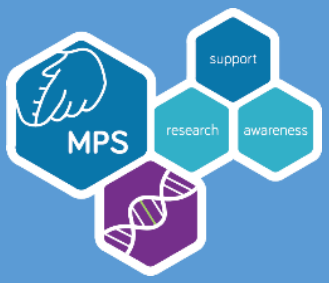
Alex Morrison, Head of Research

Tom Kenny, CEO

MPS Society

Sophie Thomas, Head of Patient Services

March 2020



Rare Disease Research Partners

BACKGROUND

The elosulfase alfa Managed Access Agreement (MAA) began in December 2015 with the aim of collecting more data on the effects of treatment in clinical practice over a five-year period. Response to treatment is assessed by clinical and patient reported outcome (PRO) measures (1).

The clinical outcome measures are:

- 6-minute walk test or 25ft ambulation for endurance
- FEV1 and FVC for respiratory function
- Ejection fraction for cardiac function
- Urine keratan sulfate

The PRO measures used are:

- MPS-HAQ
- EQ-5D-5L
- Beck Depression Inventory
- Brief Pain Inventory/Adolescent Paediatric Pain Tool

Patients and their caregivers have reported treatment effects other than those collected by the clinical and PRO measures. The aim of this roundtable discussion was to determine if healthcare professionals involved in the care of patients on the MAA had observed additional treatment effects.

METHODS

A roundtable meeting was held to discuss the benefits of treatment seen in clinic that fall outside of the clinical and PRO outcome measures specified in the MAA. Metabolic consultants and specialist nurses from the seven Lysosomal Storage Disorder specialist centres participating in the elosulfase alfa MAA were invited to the meeting, held in January 2020.

The discussion was recorded and transcribed. The transcript was analysed for key themes of treatment benefit using an inductive approach. Only treatment effects that are not measured in the MAA are reported here.

ATTENDEES

Participants from the following centres attended the meeting:

- Birmingham Children's Hospital
- Central Manchester Foundation Trust
- Great Ormond Street Hospital
- Royal Free Hospital
- University College London Hospital

Centres unable to attend were:

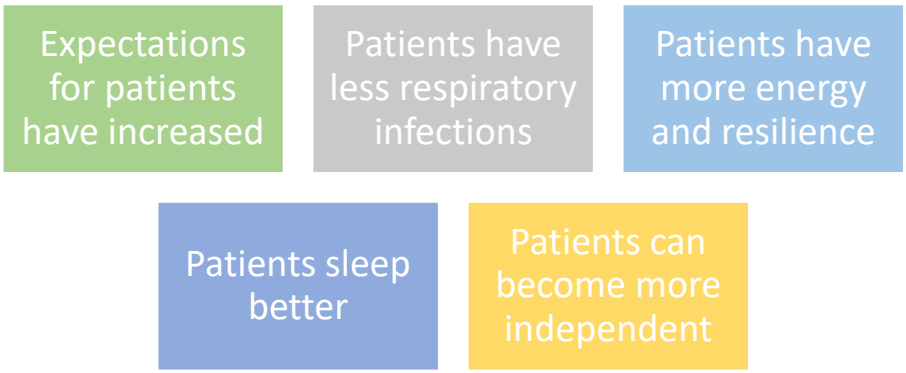
- Salford Royal Hospital
- Queen Elizabeth Hospital, Birmingham

KEY FINDINGS

The participants identified five key areas of improvement seen in patients treated with elosulfase alfa that are not captured by the existing MAA measures. The most striking observation was that their expectations for patients have changed dramatically since the introduction of this therapy. Patients are now expected to be well for longer and plans can be made for long-term management to support them through education and working life.

Treatment appears to have a significant impact on reducing the number of respiratory infections that patients experience. Patients have more energy and resilience and they sleep better. This supports children in their school attendance and being able to participate in activities. Adults are more able to socialise, work and undertake the regular activities of daily life. These improvements support patients' ability to attain independence.

KEY THEMES



TREATMENT EFFECTS

Improved life expectations	
Patients report feeling better and life expectations have improved	○ Individuals with the severe form of MPS used to have a life expectancy of 20 to 30 years ○ Patients are now in better condition, therefore they may live longer ○ Clinicians' language to parents has changed because of enzyme replacement therapy, as they are now expecting patients to be better ○ Expectations for their future have increased. Clinicians will now talk about university and work ○ There are examples of patients going to university independently and having their infusions there
More surgeries are considered	○ Major surgeries (e.g. tracheal reconstruction) are considered, which would not have been the case 10—15 years ago ○ Surgeries may have a long term benefit, as patients survive longer

Patients own expectations	○ Patients themselves have better and higher expectations for quality of life
Patients have less respiratory infections	
Paediatric patients	○ In one paediatric centre it was noted that with most of the MPS treatments, there are less respiratory infections ○ Another paediatric centre had not seen this effect, as many of their patients are very young and may not have got to the stage of recurrent respiratory infections. Recurrent ear infections are more common in the young, recurrent respiratory infections occur as patients get older
Adult patients	○ Adult patients have noticeably fewer respiratory infections, including patients in wheelchairs who are more at risk of these infections
Severe patients	○ For one centre, the effect on respiratory infections did not become apparent until the MAA, when more severe patients received treatment. Patients who would report taking antibiotics at every clinic visit were now reporting no antibiotic use

Patients have more energy and resilience	
Paediatric patients	○ Paediatric patients and parents report increased energy as an immediate effect, within a week or two of starting, and it is sustained ○ Children are taking up physical activities they were not able to do before and their school attendance is better
Adult patients	○ Adults have individual stories – e.g. patient able to return to PhD programme, patient giving up desk job to pursue further education ○ They are reporting increased resilience, meaning they: ○ Can do their shopping ○ Can perform activities of daily living ○ Can go out after work instead of staying home every evening ○ Do not have to rest as much ○ Do not have to use a wheelchair as much, can walk more ○ Are able to maintain full time employment

Patients sleep better	
Paediatric patients	○ Parents report that children have more energy and are doing more because they are less tired ○ Children are sleeping better, waking less at night

Adult patients	○ Adults are reporting this in a different way – they are able to socialise more

Patients can become more independent	
Paediatric patients	○ Some patients have become more independent and resilient through treatment ○ One patient on the trial went from being carried to travelling independently to London on public transport ○ A mother wrote recently how her child is able to travel to secondary school independently https://www.thetelegraphandargus.co.uk/news/18018115.super-drug-making-difference-otley-boy-sam/
Adult patients	○ Many of the adults are independent, with relationships and jobs

REFERENCES

1. National Institute for Health and Care Excellence. Managed Access Agreement. Elosulfase alfa for treating mucopolysaccharidosis type Iva. November 2015. Available at: https://www.nice.org.uk/guidance/hst2/resources/managed-access-agreement-december-2015-2238935869 (Accessed on 4th March 2020).

Rare Disease Research Partners

PATIENT AND CAREGIVER EXPERIENCE OF TREATMENT WITH ELOSULFASE ALFA UNDER THE MANAGED ACCESS AGREEMENT

RESULTS OF A SYSTEMATIC COLLECTION OF ANECDOTAL REPORTS OVER A THREE YEAR PERIOD

AUTHORS:

Rare Disease Research Partners

Alex Morrison, Head of Research

Sam Wiseman, Managed Access Agreement Co-ordinator

Christine Fortune, Research and Communications Associate

DATE:

5th March 2020

BACKGROUND

Elosulfase alfa has been available to patients with MPS IVA in England since December 2015 under a Managed Access Agreement (1). Patients are monitored for clinical outcomes and quality of life is assessed using the MPS HAQ, EQ-5D-5L, Adolescent Paediatric Pain Tool/Brief Pain Inventory and the Beck Depression Inventory.

While talking to patients and their caregivers and analysing their testimonies during the first NICE HST for elosulfase alfa, **it became apparent that they were reporting a number of treatment effects that may not be directly collected during the clinical and patient reported outcome** (PRO) monitoring included in the Managed Access Agreement (MAA).

Rare Disease Research Partners (RDRP) have been responsible for collecting PRO data throughout the MAA. During the routine PRO interviews with patients and caregivers to collect MAA data, we undertook independent research to collect the broader effects of treatment reported and to determine treatment effects that may be missed by the measures included in the MAA.

METHODS

COLLECTION OF PATIENT EXPERIENCE REPORTS

- Patients aged 18 years or over and caregivers of younger patients, enrolled on the MAA in England, were eligible to take part
- Participation was optional, and informed consent was obtained from patients/caregivers to take part in this additional research
- Patient experience reports were collected at 4, 8, 12, 24 and 36 months of treatment under the MAA for patients who entered the MAA treatment naïve
- Patients who had been treated with elosulfase alfa prior to the MAA completed reports at 12, 24 and 36 months after enrolment on the MAA

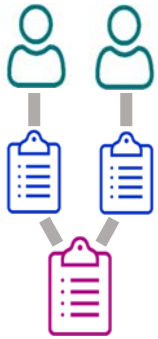
A collection form was designed to capture patient experience. These forms were completed at the end of the routine individual telephone interviews during which the MAA PRO data was collected. Patients /caregivers were asked different questions based on their treatment status at entry to the MAA and length of time on the MAA.

Patient type	Question	Time point
Naïve patient in first year of MAA	Have you noticed any changes since starting treatment?	4, 8 and 12 months
Prior treatment patients and naïve patients after one year on the MAA	Have you noticed any changes in the last 12 months?	Prior treatment patients at 12, 24 and 36 months Naïve patients at 24 and 36 months

- The patient experience reported by respondents was hand written onto the collection form by the RDRP interviewer and then transferred to a database
- Individual reports were sent to the respective responder for verification of accuracy and any amendments necessary were made in the database
- Results of the reports collected from December 2015 to December 2019 are reported here

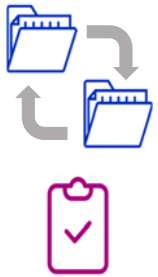
ANALYSIS METHOD

- Qualitative analysis was performed by two coders using an inductive thematic analysis with open coding (Figure 1)



The reports database was analysed by two coders using a thematic analysis with open coding. Both coders read through all reports independently, identified themes and added them to a code list.

The two code lists were used to create a master code list of themes and sub-themes which the coders discussed and came to an agreement on.



Reports were divided into two sets and each coder added primary coding to one set based on the agreed master list.

The coders then switched report sets and added their secondary coding to this second set. Any discrepancies between coders were discussed and resolved to finalise the coding.

RESULTS

SURVEY RESPONSES

53

Total patients

A total of 53 patients consent to take part in the study

31

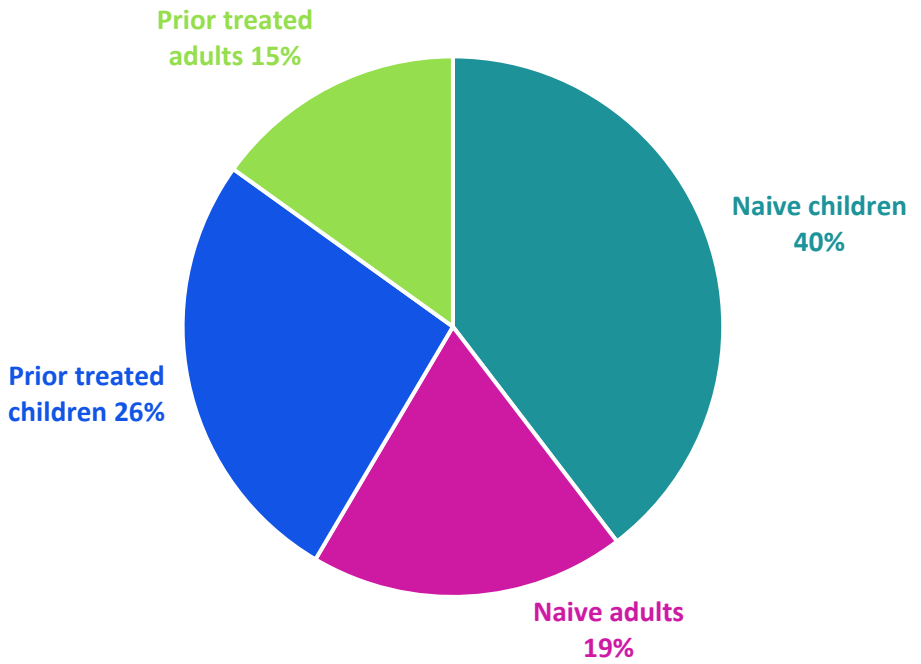
Naïve patients

31 naïve patients (21 children, 10 adults)

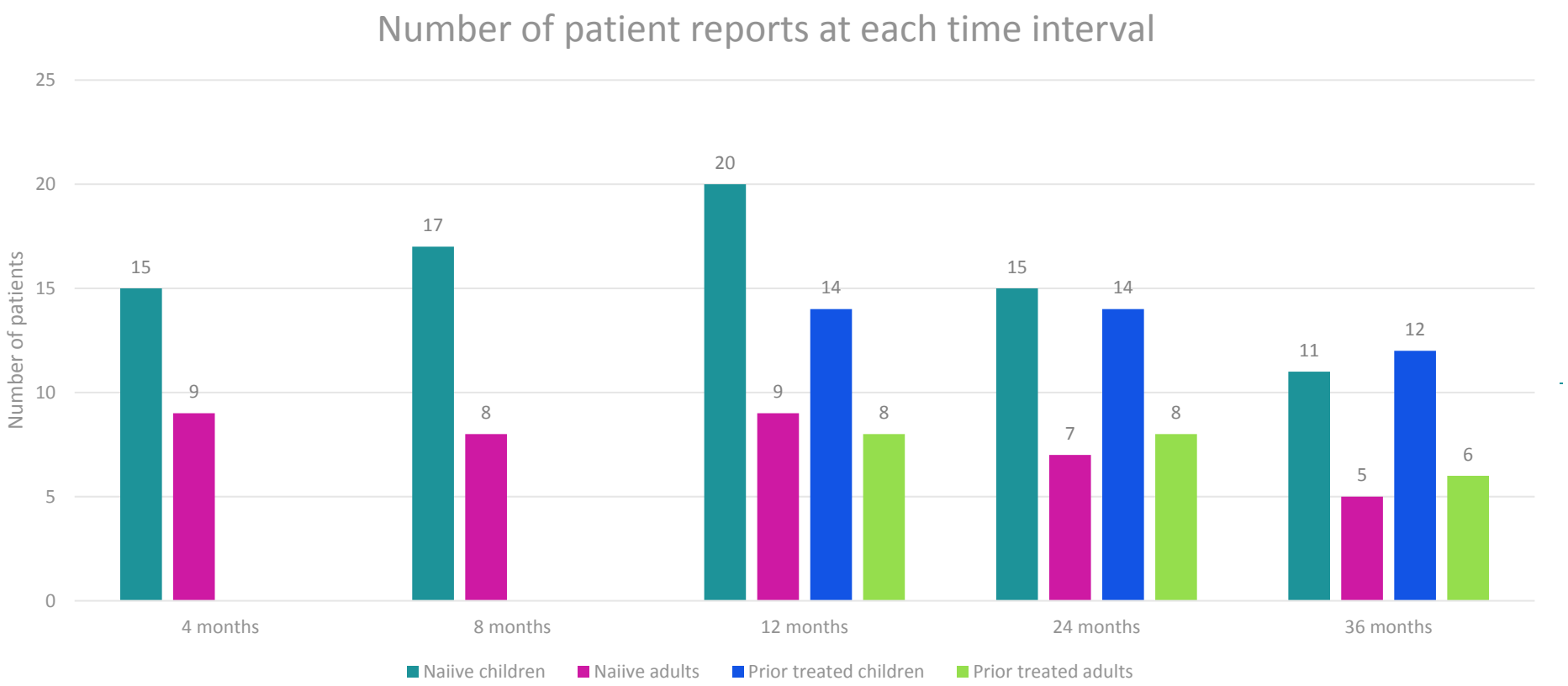
22

Prior treated patients

22 prior treated patients (14 children, 8 adults)



- We collected a total of 182 reports for these 53 patients
- Not all patients provided testimony at every time point

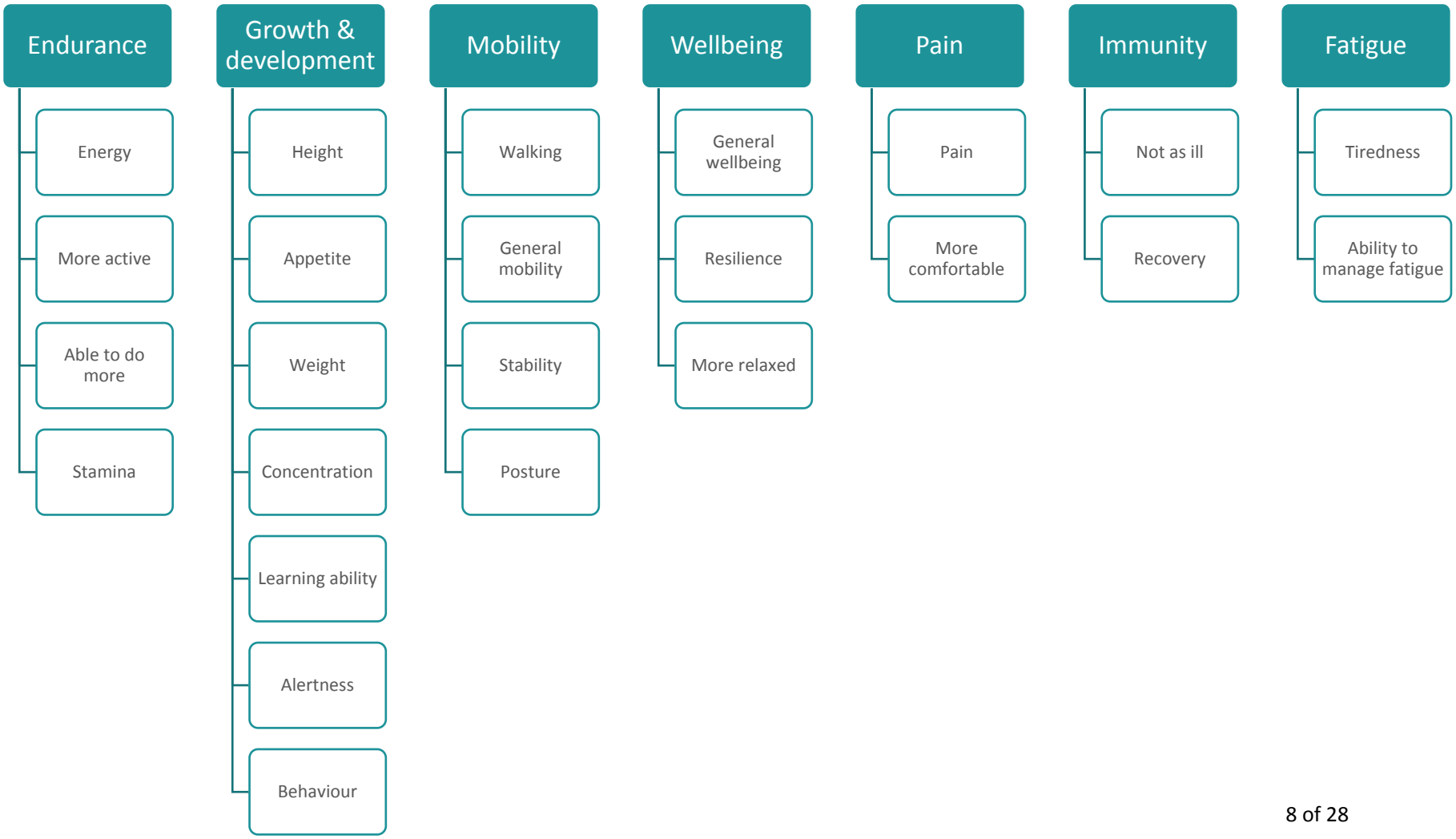


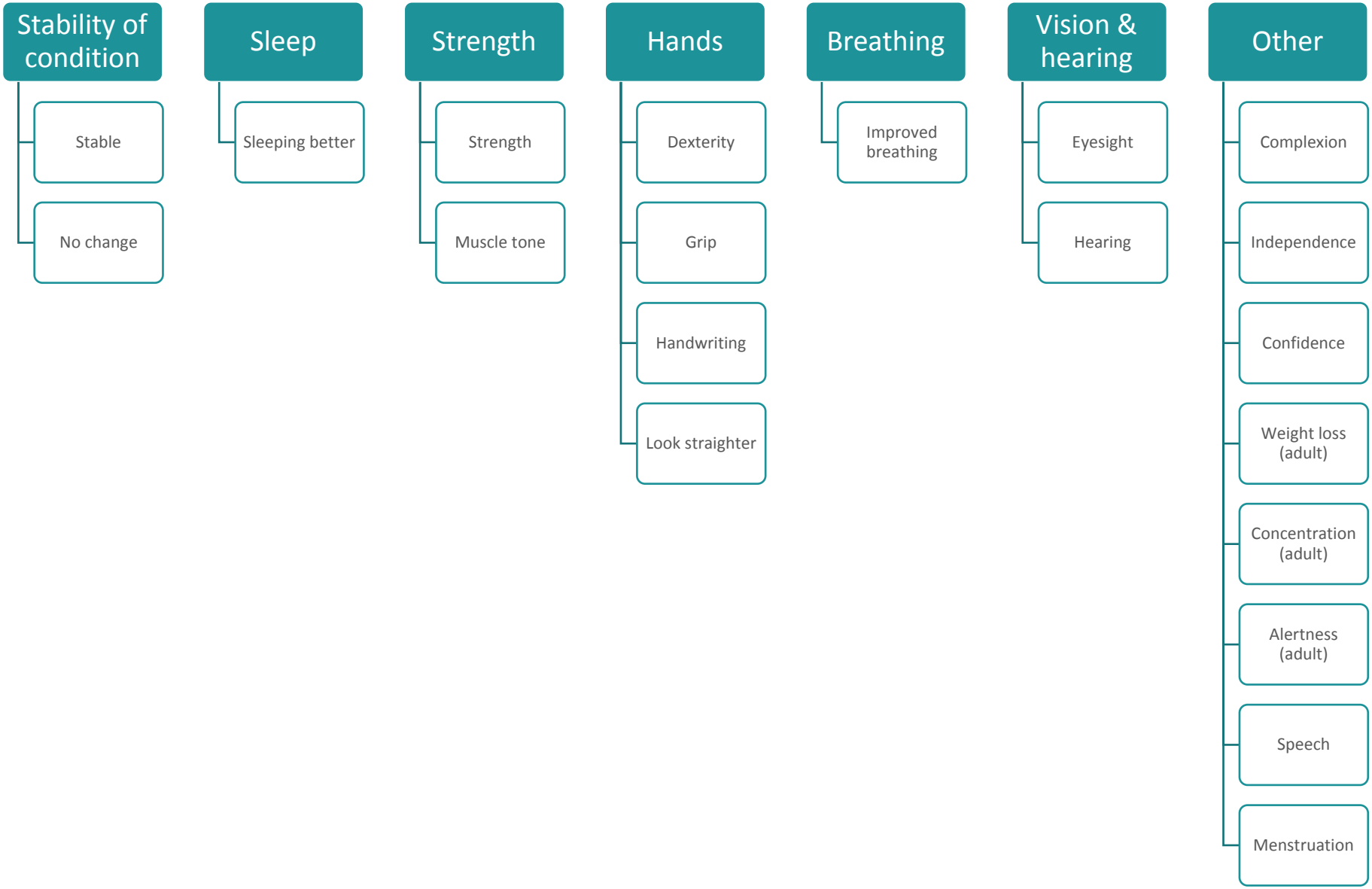
PATIENT DEMOGRAPHICS

	Range	Mean	Median
Patient age at entry to MAA	1 — 58 years	16 years	12 years
Time on treatment (naïve patients)	1 year, 2 months — 4 years, 1 month	3.2 years	3.6 years
Time on treatment (prior treated patients)	7 years, 2 months — 10 years, 9 months	9.1 years	8.5 years

THEMES OF TREATMENT BENEFIT

- **A total of 14 broad themes were identified**, with 44 subthemes
- Improved endurance was the most common theme overall
- Stability of their condition was more frequently mentioned by prior treated patients
- Improvements in growth and development, mobility, wellbeing, pain, immunity and fatigue were commonly reported across groups




Stability of condition
Stable
No change
Sleep
Sleeping better
Strength
Strength
Muscle tone
Hands
Dexterity
Grip
Handwriting
Look straighter
Breathing
Improved breathing
Vision & hearing
Eyesight
Hearing
Other
Complexion
Independence
Confidence
Weight loss (adult)
Concentration (adult)
Alertness (adult)
Speech
Menstruation

THEME: ENDURANCE

More active, more energy, able to do more, more stamina

- Endurance was the most common theme expressed by patients and caregivers overall
- Improvements in endurance were reported in patients of all ages, child and adult

Improved endurance means not having to plan your day around your energy levels

"My energy levels have greatly increased and my stamina has improved.

I am now much more active during the day and no longer need to schedule things to do based on the time of day or if I have something planned for the same day e.g. can go out at any time without worrying if I will become too tired and will need to rest when I return home.

Previously I would have to plan my daily activities more to avoid overtiring.

I am much more active around the house and also go out more to do shopping, run errands for others etc.

I enjoy being out much more as I now know that when I return home I can still do other things and not feel overtired."

(Naïve Adult – 12 months on treatment)

"Better able to work in team, not worrying about where they are going for lunch as an example and whether will have the energy to get there."

(Prior treated adult – 12 months on MAA, 8 years on treatment)

Improved endurance allows patients to take part in leisure activities

"Started doing PE - didn't do any last year and now doing 2 lessons a week. In summer had a lead role in 'Play in a Week' which included a 1-hour performance without her wheelchair and before would not have been able to do this as 5-10 minutes out of the wheelchair and she would have been tired. More time out of wheelchair, started riding her tricycle"

(Prior treated child – 10 years on treatment)

"Energy levels have increased. In school holidays - attends Milwall's disability football club (2-3 hours) has energy to do this.

(Naïve child – 12 months on treatment)

Improved endurance lets patients do more and attempt new things

"When I have treatment - have more energy, able to hold myself up. Could get off floor without holding on to anything, but after missing 3 weeks' treatment needed to hold onto something again"

(Naïve Adult – 4 months on treatment)

"Energy levels/endurance/ walks improved. Energy after school to play for 2-3 hours. Used to use buggy/carried. Now happy to walk 50-100m on her own (slowly)."

(Naïve child – 4 months on treatment)

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

(Naïve child – 4 months on treatment)

THEME: GROWTH AND DEVELOPMENT

Increased height, improved appetite, weight gain, improved concentration, improved learning ability, more alert, improved behaviour

- Caregivers saw a positive impact on children's growth and development

Children grew in height	Children had improved appetite and put on weight
"She has grown around 2 cm since January, only 0.5 cm in previous year." *(Naïve child – 4 months on treatment)* "Grown over 6cm." *(Naïve child – 8 months on treatment)* "Has grown 3.5 cm and put on weight" *(Naïve child – 12 months on treatment)* "Was 91cm last year and is now 94cm" *(Naïve child – 12 months on treatment)* "Posture is good - grown +2cm since last measures." *(Prior treated child – 2 years on MAA, 7 years on treatment)*	"Increased appetite, increase in variety of food, has become less fussy." *(Naïve child – 12 months on treatment)* "Put on weight, up a clothes size from age 2-3 now 3-4 years" *(Naïve child – 12 months on treatment)* Gone up in clothes size from 2-3 years to 3-4 years. Weight up by 1.5kg in one year." *(Naïve child – 12 months on treatment)*

Children's ability to learn improved

"Increased vocabulary, wants to learn, increased concentration, hand-eye coordination has improved"
(Naïve child - 4 months)

"Concentrating at school has increased, didn't feel as tired. Fine motor skills - have not noticed any difference. Builds Lego."
(Naïve child – 12 months)

"Moved up two grades in school, more attentive/alert"
(Naïve child – 12 months)

"Handwriting has improved a bit. Concentration improved (Patient is autistic)
(Non-Naïve child – 12 months on MAA, 7 years on treatment)

"He is continuing to develop cognitively in some areas, at a very slow pace. He is able to engage and make eye contact more now, than a year ago."
(Naïve child – 12 months)

"His vocabulary has improved - school have noticed this"
(Naïve child – 24 months)

"Mental age improving, started writing e.g. a b c, following commands"
(Non-naïve child – 24 months on MAA, 5 years on treatment)

*"*Cognitive development improved. School report shows: social skills improved, engaging with other students, vocabulary improved."
(Naïve child – 36 months)

THEME: MOBILITY

Improved walking, maintained walking, improved general mobility, maintained general mobility, more stability, better posture

- Patients report short and long-term benefits to mobility

Children may become less reliant on being carried and using pushchairs	Patients are more able to walk	Adults report continued mobility benefits over time	Improvements to mobility can reduce caregiver burden
"More content to walk and asking less to be carried. Very noticeable when Father takes him to the shops after school" *(Naïve Child – 8 months)* "Large improvement in mobility. Before infusions was heavily reliant on buggy, but increasingly able to walk" *(Naïve child – 12 months)*	"Moves more freely. Walks further." *(Naïve Child – 12 months)* "Can now move more freely and walk longer again without tiring, meaning they spend more time enjoying life." *(Naïve child – 24 months)* "Has impacted on walking – improving." (Naïve adult – 8 months)	"Not as stiff." "Mobility much better." (Naïve adult at 4 and 8 months of treatment respectively) "Been on treatment for 5 years now. Last 12 months has been very stable with no deterioration in mobility or energy levels." (Prior treated adult – 12 months on MAA, 4 years on treatment)	"Significant improvement in mobility. Less strenuous to move." *(Naïve child – 36 months)*

- Some patient reports demonstrate an improvement in mobility over time
- This example is from a naïve patient who started treatment aged 20 years

4 months of treatment	• "Finding it easier to move. Used to find it difficult to crawl, but now can crawl with less pain."
8 months of treatment	• "Able to transfer from/to wheelchair better. Move a bit more than used to."
12 months of treatment	• "Move a lot better. Able to transfer better from a chair to a sofa."

THEME: WELLBEING

Improved wellbeing, maintained wellbeing, improved resilience, more relaxed

Patients wellbeing is enhanced by treatment

"Seems happier in himself, more life about him."
(Naïve child – 8 months on treatment)

"More positive outlook, more engaged with people and things."
(Naïve adult – 8 months on treatment)

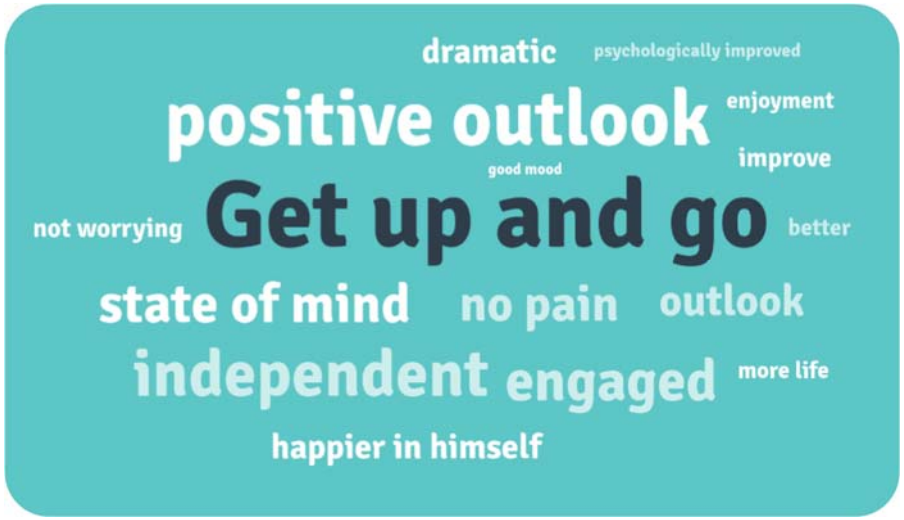
"Happier in herself, in a good mood a lot more of the time."
(Naïve patient – 4 months of treatment)

"More enjoyment. Has been on treatment for 4 years and is more independent including state of mind i.e. not worrying about pain."
(Prior treated adult – 12 months on MAA, 5 years on treatment)

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

"Overwhelmingly positive. 3-4 months into treatment things started to improve dramatically. Feels positive and better than has been in years. No pain. No negative consequences to treatment"

(Naïve adult – 8 months on treatment)



Less pain, more comfortable

Patients report less pain

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

"Since starting Vimizim, a little stronger, used to cry as had pain in knee, does not anymore."
(Naïve child – 4 months)

"Not in as much pain the day after a busy day."
(Naïve adult – 24 months)

"Reduced amount of pain medication"
(*Naïve child – 4 months*

"Does not mention pain in hand anymore"
(Naïve child – 8 months)

"Not complaining about pain in knees"
(Naïve child – 8 months)

"Not been waking up in the night in pain."
(*Naïve adult – 4 months of treatment)*

Pain medication may be reduced

"Not taking medication for pain anymore - stopped end of September"
(Naïve adult – 4 months)

"Reduced amount of pain. No painkillers in the last 2-3 months whereas before it was more or less daily"
(Naïve adult – 8 months)

Patients have fewer illnesses and infections

"Immune system stronger - mum cannot remember last time she had a chest infection."
(Naïve child – 12 months on treatment)

"Infections/being poorly/going to hospital- no antibiotics in last 2 years. Used to be every 6-12 weeks and sometimes twice in a month."
(Naïve child – 36 months on treatment)

"Before Vimizim used to experience diarrhoea. Since taking Vimizim this has stopped."
(Prior treated adult – 12 months on MAA, 7 years on treatment)

"Used to be sick in night (at least once a week, now only happened once in the last year)."
(Naïve child – 12 months on treatment)

"Has had bugs but fights them off better than before, improved immunity."
(Naïve child – 36 months on treatment)

"No health issues (e.g. chest infections) in last 12 months."
(Prior treated child – 36 months on MAA, 7 years on treatment)

"Recovering quicker from colds."
(Prior treated adult – 36 months on MAA, 8 years on treatment)

"No chest infections since starting Vimizim treatment."
(Naïve adult – 36 months on treatment)

"No colds/chest infections since starting treatment. Used to bring phlegm in the morning but now lungs are clear"
(Naïve adult – 8 months)

Better health - hay fever gone, use to have a raised temperature a lot of the time, but not now as much, not sick as much"
(Naïve child – 8 months)

"Colds don't progress to her chest anymore and go away quicker. Doesn't get ill so easily."
(Naïve child – 24 months)

"Doesn't fall ill as often. In the past, he would get bronchitis, flu, colds, not so much in the last year."
(Naïve child – 24 months)

THEME: FATIGUE

Less tired, ability to manage fatigue

Patients experience less fatigue	Children are more able to cope with schooling	Less fatigue allows patients to do more
"Does not get tired as quickly" *(Naïve child – 8 months)* "Used to be tired, complaining of being tired, not now" *(Naïve child – 12 months)*	"Used to be very tired at end of school day, now bright and perky" *(Naïve child – 4 months)* "Concentrating at school has increased, didn't feel as tired." *(Naïve child – 12 months)*	"Involved in more activities / less tired" *(Non-naïve child – 24 months)* "I am able to do things without planning ahead so to avoid over tiring." *(Naïve adult – 24 months)* "More enjoyment, able to do more as not as tired." *(Prior treated adult 12 months on MAA, 8 years on treatment)*

Stable, no change

Patients feel that their condition has been stabilised	"Been on treatment for 5 years now. Last 12 months has been very stable with no deterioration in mobility or energy levels" *(Non-naïve adult – 12 months on MAA, 5 years on treatment)* "Maintained energy and stamina. Generally, well, has had no serious chest or ear infections, had these a lot when younger. Maintained mobility" *(Non-naïve child – 12 months, 7 years on treatment)* "Nothing new, same benefits as last year. Nothing getting worse" *(Naïve adult – 24 months)* "No changes, but remaining stable which is an improvement on pre-treatment" *(Non-naïve adult – 36 months on MAA, 7 years on treatment)*

THEME: SLEEP

Sleeping better

Patients sleep better

"Doesn't scream in night anymore"
(Naive child – 8 months)

"Better quality of sleep"
(Non-naïve adult – 12 months, 4 years on treatment)

"Doesn't wake up in the night now. Was snoring before treatment but now doesn't snore/very rarely snores now (positional). Quality of sleep improved"
(Non-naïve child – 12 months, 7 years on treatment)

Sleep is much better and is regulated, gets up and falls asleep at same time each night."
(Naïve adult – 12 months)

Nightmares have stopped, is a different child since treatment."
(Naïve child – 36 months)

"My sleeping is better and I have noticed that recently whatever time I wake up, I do not feel the need to go back to sleep, e.g. I sometimes have to set the alarm for very early and after getting ready. I do not feel sleepy again until night time. I feel that by sleeping better, I am much more alert during the day. I had a sleep study test in this last year and they have said it is still ok, and that I do not wake up throughout the night."
(Naïve adult – 24 months)

"No longer on CPAP. Dec 2015 - diagnosed sleep apnoea, Apr 2015 - started Vimizim treatment, Dec 2017 - No longer need CPAP, not snoring, not waking up during the night"

(Naïve Adult – 24 months)

THEME: STRENGTH

Increased strength, improved muscle tone

Patients feel stronger

"Improvement in energy levels and strength."
(Naïve adult – 8 months)

"Feeling stronger."
(Naïve adult – 8 months on treatment)

"Can do things better - like open a packet of crisps (wrists/hands stronger)."
(Naïve adult – 12 months)

"He is also getting stronger physically, and can pull himself to stand for short periods of time. "
(Naïve child – 12 months)

THEME: HANDS

Improved dexterity, better grip, improved handwriting, hands look straighter

Improvement in patient's hands

"Use of hands slightly improved - other family members have MPS IV, based on their hand mobility, his is better." *(Naïve child – 24 months)*

"Hand grip has improved."
(Prior treated adult – 36 months on MAA, 10 years on treatment)

"Hands look straighter."
(Naïve child – 12 months)

"Wrist is less flexible which means a better grip than before."
(Naïve adult – 4 months)

THEME: BREATHING

Improved breathing

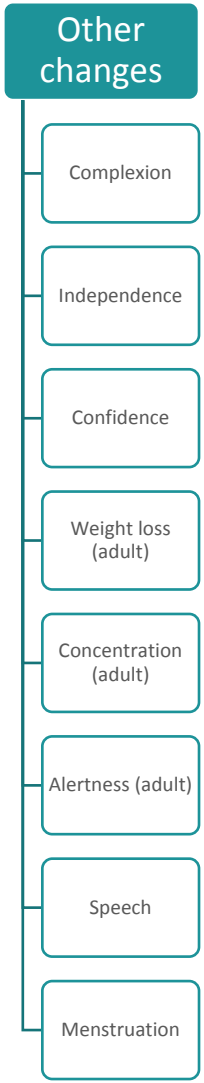
Patients breathing is improved
"Other people have noticed breathing better. Now not breathless and tired after shower" *(Naïve adult – 4 months)* "Use to have breathing problems and vomited during the night, now gone completely." *(Naïve child – 8 months)* "Breathing improved." (Naïve adult – 8 months)

THEME: VISION AND HEARING

Improved eyesight, maintained eyesight, improved hearing

Patients eyesight and hearing is stable or improved
"Hearing stable, slightly improved, wears hearing aids" *(Non-naïve child – 12 months)* "Eyes are better, glasses not as strong as previous prescriptions" *(Non-naïve child – 12 months)* "Corneal clouding improved." *(Naïve child – 24 months)* "Corneal clouding is now negligible (only appeared when he came off treatment) *(Non-naïve child – 24 months)*

THEME: OTHER CHANGES



- A small number of patients or caregivers mentioned other changes

- The most common of these 'other changes' mentioned by naïve patients was an improved complexion:
  - "Complexion improved a lot." (Naïve adult – 8 months on treatment)
  - "Looks better - especially in the complexion." (Naïve child – 4 months on treatment)

- Prior treated patients were more likely to mention increased independence:
  - "New walker, so now walks further than she used to, given her more independence with friend." (Prior treated child – 12 months on MAA, 7 years on treatment)

- Other reports included:
  - "Increased confidence, able to lose weight, no brain fog – especially first thing in the morning." (Naïve adult – 8 months on treatment)
  - "Speech is clearer and louder, more engaged during conversations, can sit and watch a whole film without falling asleep or losing interest." (Naïve adult – 12 months on treatment)
  - "Period started last month (had stopped for 3 years)." (Prior treated adult – 24 months on MAA, 6 years on treatment)

REPORTS OF NEGATIVE CHANGES

- A small number of patients reported negative changes including some deterioration
  - "Knees are getting worse due to condition" – *(Naive child – 8 months)*
  - "Seems to be getting more pain in knees and hips" – *(Naïve child – 12 months)*
  - "Poor mobility, fatigue, increased pain, coughing/wheezing (Asthma) has worsened & change of posture" – *(Non-naïve child – 24 months on MAA, 8 years on treatment)*
  - "Now complaining from pain in his arms, hands, legs and knees" – *(Naïve child – 24 months)*
  - "Mobility deteriorated - more knocked kneed" – *(Naïve child – 24 months)*
  - "Slowed down. Things are a little harder. Increased pain relief medication is used" – *(Naïve adult – 36 months)*
  - "Hearing reduced, natural progression of the disease so expected this" – *(Non-naïve child – 36 months on MAA, 8 years on treatment)*

- Some patients mentioned more pain or fatigue, including that experienced around infusion day:
  - "Is scheduled for a hip replacement and is in a lot of pain/fatigue." (Prior treated child – 12 months on MAA, 7 years on treatment)
  - "Pain when coming up to infusion" – *(Naïve adult – 4 months on treatment)*
  - "When patient has a cold or flu energy levels are worse than before, sometimes tired on day of infusion" – *(Naïve adult – 8 months on treatment)*

PATIENT EXPERIENCE OF TREATMENT BREAKS

- Some patients told us about their experience of coming off treatment for a period of time
- There were noticeable changes, even after short breaks in treatment
- Patients reported less energy, tiredness, pain, headaches and reduced mobility and appetitie

Off treatment for 5—6 weeks

"During Oct/Nov 2016 had 5-6-week period with only one dose due to problems with cannulation.

After 2 weeks of no dose, saw a difference.

After 4 weeks no energy left, had worn her energy out.

Eyes were bleary, had more pain, would wake up with a headache.

Once port fitted she had her sparkle back after around a month."

(Naïve child – 12 months of treatment)

Off treatment for 4—5 months

"During 4–5 months whilst not receiving Vimizim (needed port re-sited).

Vision first thing to be affected. Energy decreased. Not sleeping as well - headaches and nausea on waking morning. Appetite decreased. Emotional wellbeing decreased. More joint soreness, meaning more reliance on painkillers and difficulty moving which restricted their activities. Stopped going out with friends etc.

Now back on Vimizim, energy and stamina increased. Appetite better. Vision improved. General wellbeing improved. Can now move more freely and walk longer again without tiring, meaning they spend more time enjoying life."

(Naïve child – 24 months on treatment)

- "When Vimizim stopped walking decreased. Much better on meds" – *(Non-naïve child – 12 months on MAA, 7 years on treatment)*

Off treatment for 9 weeks	Missed a few infusions
"Condition has not deteriorated at all since first started on trial. Apart from 9 week break of treatment when felt more tired and was sleeping for longer, poor quality of sleep" *(Non-naïve adult – 12 months on MAA, 5 years on treatment)*	"Missed a couple of infusions due to a temperature. Really noticed a drop in energy levels after missing just a few infusions. It took two treatments to get back to normal energy levels" *(Naïve child – 24 months)*

CONCLUSIONS

- Patients and caregivers report a broad range of treatment effects that have an impact on their quality of life
- Increased endurance in terms of having more energy, more stamina and being able to do more is experienced by most patients on elosulfase alfa treatment
- This and some of the other treatment effects reported by patients may not have been measured by the patient reported outcome measures used in the Managed Access Agreement
- This study supports the need to consider patient testimony when assessing the impact of treatment on quality of life (QoL), particularly in rare disease where specific QoL tools are not readily available

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1. National Institute for Health and Care Excellence. Managed Access Agreement. Elosulfase alfa for treating mucopolysaccharidosis type Iva. November 2015. Available at: https://www.nice.org.uk/guidance/hst2/resources/managed-access-agreement-december-2015-2238935869 (Accessed on 4th March 2020).

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Rare Disease Research Partners

MPS IVA PATIENT AND CAREGIVER EXPERIENCE OF TREATMENT – UK SURVEY

Rare Disease Research Partners

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MPS Society

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April 2020

CONTENTS

EXECUTIVE SUMMARY

Elosulfase alfa has been available to patients with MPS IVA in England since December 2015 under a Managed Access Agreement (MAA) (1). This survey was conducted to gather additional evidence on treatment effects to support the evaluation of elosulfase alfa by NICE, following this period of managed access.

PATIENT DEMOGRAPHICS

- 42 complete responses were received, 22 (52%) from individuals with MPS IVA; 20 (48%) from parents/carers
- 84% of respondents were resident in England
- Patients ranged in age from 2–61 years of age (mean 22 years)
- The majority of patients were aged 30 years or under
- Twenty-five (60%) patients were adults, aged 18 years or older

TIME ON TREATMENT

- Patients had started treatment between the ages of 1–58 years (mean 17 years)
- 93% were still on treatment. Three patients had discontinued treatment
- Patients had received elosulfase alfa for a mean of 5.1 years (range 23 weeks to 10 years 7 months)

FIRST EFFECTS OF TREATMENT

- Increased energy and stamina, and a decrease in fatigue, were the most common first effects in patients aged 1–10 years. Effects were often seen in the first month of treatment
- Adults mostly reported an increase in energy, less fatigue, better mobility and improved physical strength
- A common feature of patients aged 31 years and over was a decrease in pain
- First positive effects from Vimizim were often seen within the initial months of treatment for all age groups

EFFECTS OF TREATMENT OVER TIME

- The effects of treatment continued and/or improved over time, regardless of how long the patient had received the treatment for, or their age
- Patients who had missed an infusion or had to have a break for medical reasons noticed a deterioration, but immediately felt an improvement when back on treatment
- Some patients receiving Vimizim for over 10 years could still see their health continuing to improve, with others feeling its continued benefit

MAIN BENEFITS OF TREATMENT

- The main benefits of treatment reported by parents of children under the age of 10 years were an increase in energy levels, less fatigue and an improvement in walking. These effects allowed the children to participate in every-day activities, such as nursery, physical play and playing with other children, which improved their quality of life
- Patients aged 10–20 years stated they had been able to go back to full-time schooling or college because of the treatment, with some children now being able to participate fully in school/college life, and in extra-curricular activities and sports
- Most patients aged 41 years and over reported an increase in energy, and an improvement in breathing
- From the age of 15 years, patients reported the effects of treatment contributed to their mental health, a benefit that became more prominent with age
- Patients also reported their colds and infections had been largely reduced, and suggested the positive effects of the treatment had given their body enough strength to have MPS IVA-related surgery

SUSTAINED BENEFITS AFTER MORE THAN TWO YEARS OF TREATMENT

- Patients on treatment for over two years continued to receive benefits, regardless of how long they had been on treatment, or age
- The benefits were sustained even in those patients receiving treatment for over ten years

IMPACT OF TREATMENT ON CHILD'S EDUCATION

- Most parents of patients under 18 reported that although, in the past, infusions were disruptive and had an impact on the number of hours their children attended education, this was resolved once infusions could take place at home or school
- Respondents of children under 18 reported their children spent more time in education after treatment as their levels of energy had increased, with children now being able to attend school full-time, and being able to partake in after school activities
- A large number of patients over 18 had attended/completed college or university. Schools and universities had always been accommodating of infusion days
- Some patients over 18 reported that treatment had played a key role in being able to complete their education as it had made them independent and had allowed them to be physically and mentally present for lessons

IMPACT OF TREATMENT ON EMPLOYMENT

- Patients reported being able to work after starting treatment, with some of them balancing part-time work and college, and some now able to work full-time without being exhausted
- Some patients that had to leave work before starting on treatment had been able to return to paid/unpaid work
- Most working parents of children on treatment were able to reduce the number of hours they worked to fit around their child's treatment. For others, their company accommodated flexible working, including working from home on infusion days
- A few mothers had initially stopped working but had returned to work part-time thereafter
- One mother stated the improvements in their child after receiving treatment, had benefited her ability to work as the child is now attending school full-time

IMPACT OF TREATMENT ON LEISURE TIME

- The positive impact on patients' leisure time was evident across all ages
- In children under 18, increased energy meant they were now able to socialise with their peers, undertake outdoor activities, attend after school activities and even participate in sports
- Infusions had not affected leisure time in children, with some finding ways to interact with their friends, remotely, while receiving the infusion
- In patients over 18, the effects of treatment also improved their social life, their ability to travel independently and to undertake new hobbies

IMPACT OF TREATMENT ON INDEPENDENCE

- Independence had improved across all ages
- This was most noticeable in patients aged 15–19 years, with these patients reporting they had been able to undertake household chores, pass their driving test, prepare meals and travel independently
- Some patients reported treatment had not had any impact on their independence
- Adult patients stated an increase in independence had meant more socialising and going out, and were now able to travel by themselves and do their own shopping

DISADVANTAGES OR PROBLEMS WITH TREATMENT

- The main disadvantages for families of patients on treatment were not being able to take long holidays, scheduling around infusion days and infusions being time consuming
- A large number of patients and parents/caregivers said there were no problems or disadvantages with the treatment
- A few logistical problems had been encountered with the home delivery of elosulfase alfa and the availability of nurses
- Other reported issues included unsuitable veins, tiredness post-infusion and minor reactions
- Some patients said all these disadvantages are outweighed by the benefits of the treatment

THOUGHTS ABOUT THE MANAGED ACCESS AGREEEMENT

- Consensus in all responses about the MAA was that parents/patients would do anything to keep receiving treatment with elosulfase alfa
- Patients/parents were aware the MAA is the only way of getting treatment with elosulfase alfa and were worried about its future availability
- There were concerns about the way the clinical measures decide if the patient continues treatment, and believed criteria looking for constant improvements does not reflect this degenerative disorder

BREAK IN TREATMENT

- Patients health deteriorated as soon as they took a break in treatment, even when the break was as short as one week, or when missing one infusion
- Patients felt fatigued, their stamina decreased, breathing problems and pain returned, and vision deteriorated. Mobility decreased, with at least two patients having to go back to using a wheelchair

EDUCATION/EMPLOYMENT OF PATIENTS WITH MPS IVA

- The majority of patients (83%) were in education, employed or retired following a long career
- Only two patients were unable to work due to their health

SELECTION OF FURTHER COMMENTS

- **The treatment has helped my child a lot,** and I think it will keep helping him in a longer term.
- I never miss my treatment as it keeps me going, **can't live without it as is so good.**
- **Life changing in every possible way and magical for my child.**
- **Being on Vimizim has given my son the best possible start in life**
- **We need this treatment** to continue to give our child the **best chance of a longer life**.
- **Vimizim gives hope where there is none.**
- If he had not been on treatment […] **his quality of life would be significantly lower.**
- **Vimizim has played a crucial role in her life**. **I never imagined she would go to** University **and be** independent**.**
- **Please allow us to keep accessing the drug that has changed our lives and given us a life.**
- It was the **best thing that has ever happened to me.**
- **I'm a bit scared of losing the treatment**, as I'm finally […] working well doing stuff I love, and I worry that if I lose Vimizim **my energy levels will go down again, and that I perhaps** won't be able to keep up in work further.
- When Vimizim came about it was a ray of hope, **to see yourself improve** when all you know is bad news it has been amazing, and I worry less about the future.
- **It feels like I have been given a second chance.** I see life now as an opportunity to find meaning and enjoyment.
- **It has made me a new man** and I am scared that I will go backwards if stopped**.**
- **Life changing.** It has given me a new lease of life that I have never experienced before.
- **I can't imagine a future without Vimizim**.

THE SURVEY

Elosulfase alfa has been available to patients with MPS IVA in England since December 2015 under a Managed Access Agreement (MAA) (1). This survey was conducted to gather additional evidence on treatment effects to support the evaluation of elosulfase alfa by NICE, following this period of managed access.

METHODS

The questionnaire was designed by the MPS Society and Rare Disease Research Partners (RDRP) (Appendix I). The survey was advertised to members of the UK MPS Society with MPS IVA and patients on the elosulfase alfa managed access agreement via e-mail and MPS Society social media accounts. Respondents were asked to complete the on-line survey which was available for one week in January 2020.

The survey was open to any patient with MPS IVA aged 16 years or over, or parent/caregiver of a patient with MPS IVA. Only patients who was currently receiving treatment with elosulfase alfa or had ever received this treatment in the past were included. Individuals and their parent or caregiver could both take part.

The survey was open to participants across the UK and therefore included some patients receiving elosulfase alfa outside of the MAA in England.

Responses were collected anonymously, and respondents were asked to provide consent for their data to be shared.

Patient ages are reported as ranges to protect individual patient anonymity.

RESPONSES

We received 42 complete responses to the survey, 22 (52%) from individuals with MPS IVA and 20 (48%) from parents or caregivers.

Most respondents (84%) were resident in England (Figure 1).

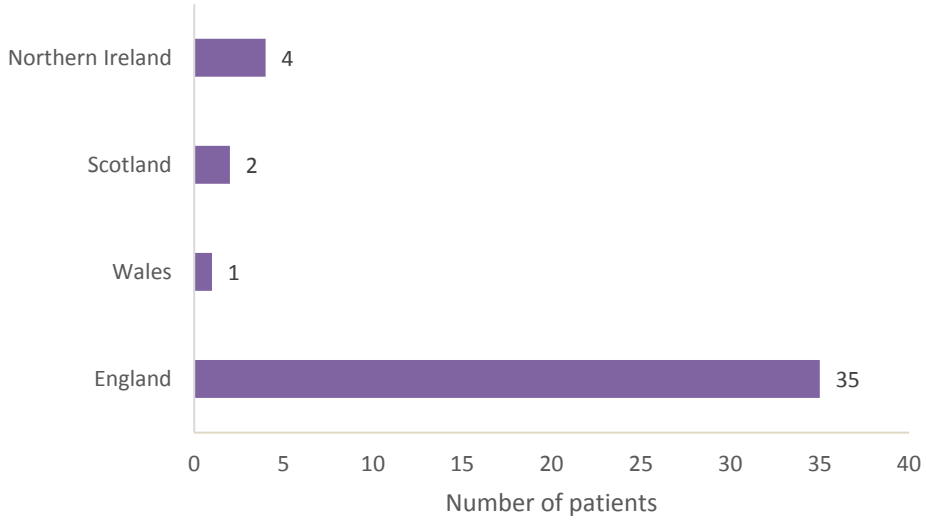


FIGURE 1. COUNTRY OF RESIDENCE

PATIENT DEMOGRAPHICS

Patients ranged in age from 2–61 years of age (mean 22 years). The majority of patients were aged 30 years or under (Figure 2). Twenty-five (60%) patients were adults, aged 18 years or older.

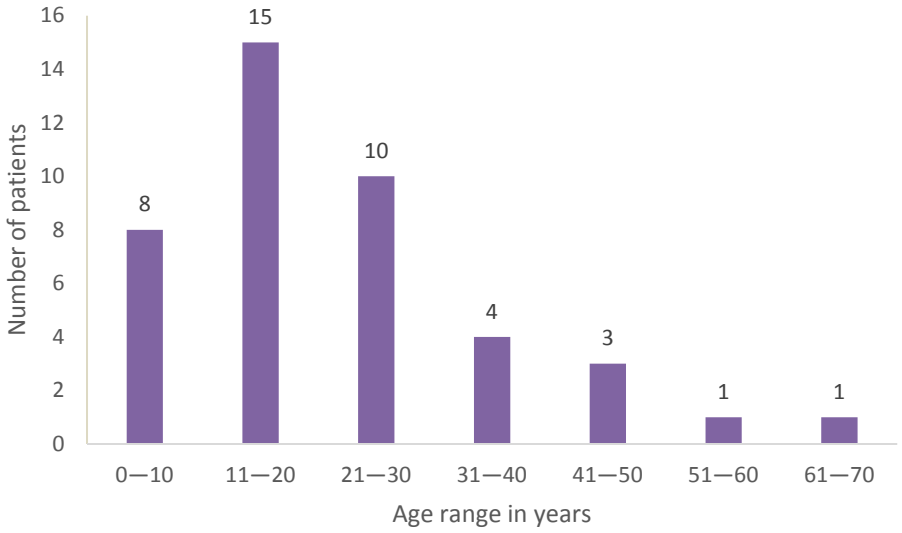


FIGURE 2. PATIENT AGE

TIME ON TREATMENT

Patients had started their elosulfase alfa treatment between the ages of 1–58 years (mean 17 years). Most (93%) were still on treatment, while three patients had stopped treatment. Those patients still on treatment had received elosulfase alfa for a mean of 5.1 years (range 23 weeks to 10 years 7 months).

FIRST EFFECTS OF TREATMENT

We asked: Thinking back to when you first started Vimizim treatment, what effects of treatment did you first notice and how soon after starting treatment did you notice these effects? This can include any positive or negative effects you/your child experienced.

- Increased energy and stamina, and a decrease in fatigue, were the most common first effects in patients aged 1–10 years. Effects were often seen in the first month of treatment
- Adults mostly reported an increase in energy, less fatigue, better mobility and improved physical strength
- A common feature of patients aged 31 years and over was a decrease in pain
- First positive effects from elosulfase alfa were often seen within the initial months of treatment for all age groups

First effects of treatment in children aged 1–5 years at treatment start ***(Parents' response)***	**How soon?**	**Impact on**
At the very start we did not notice any difference, but as time passed, we started seeing some positive effects like the level of energy was increased, after his 3rd infusion.	One month	Energy
After two treatments you could tell he had more energy and posture of movement was a lot better.	One month	Energy
He had more energy, his sleeping pattern was better, slept for longer.		Energy Sleep
Within a few weeks (3/4), much greater energy levels were apparent, and continued to rise. He now has much more energy throughout the day. This has had a very positive effect on his ability to walk, talk and generally get involved a lot more with daily activities, he is a much happier child now. There have been no negative effects.	One month	Energy Mental health Walking
She started very young at 3 years. So, it does not appear like she has deteriorated.		Disease progression
Less recurring infections and use of antibiotics; Less pain; More energetic; More appetite.		Appetite Energy Infections Pain
More energy; His walking tests at hospital were improving; His lung function tests at hospital were improving; Sleep apnoea improved; No longer napped during the day.		Energy Sleep Walking
He was very young when he started treatment. The first thing we noticed were his movements become less stilted and more fluid - he moved around much easier and with less discomfort. He could get up from the floor much easier and very quickly became confident in physical activities that he wouldn't have been able to do previously, e.g. climbing, jumping etc. This change happened very quickly, within a matter of weeks. He also has lots of energy and did not tire easily, which remains true to this day.	One month	Energy Fatigue Mobility
More subtle in our daughter - not the immediate increase in energy we see with our son. When she started on treatment, she just looked healthier. Was less upset and unsettled, slept better and was happier. The effects of the condition were not so apparent in her at 4 and she was fairly active anyway.		Energy Mental health Sleep

First effects of treatment in children aged 1–5 years at treatment start ***(Parents' response)***	**How soon?**	**Impact on**
We noticed a significant increasing of energy level after my child received Vimizim treatment. She could not walk for more than 2 minutes in one occasion and cried for pain and fatigue before starting treatment; after began the treatment she started to walk and move around more without complaint about her pain (she can play and study whole day without showing fatigue often and is able to walk longer than 6 minutes). Another significant change is her strength of big muscle movement such as jumping, skipping, climbing which she could not able to complete these movements before, but after the treatment she can, and she noticed her ability of doing these movement has been changed in positive way. Also, noise from breathing and night-time sleeping disturbance episode was significantly reduced and we noticed the cases of her upper-respiratory infections were reduced. She is able to complete more self-care tasks than before.		Breathing Energy Fatigue Illness Independence Pain Self-care Sleep Strength
My child had lots more energy that we noticed after the second infusion. She has continued to grow and still has more energy now than I think she would have without the treatment. Her corneal clouding has almost disappeared- something which her optometrist can only put down to the treatment as this would not happen on its own.	One month	Energy Eyesight Growth
My son didn't like the infusions/needles and didn't understand why he was having it. There were no obvious sign of benefit and I was aware of his unhappiness. He did have reactions like nose bleeds and rashes, but I'm not 100% convinced they were associated with Vimizim.		Mental health
Increased stamina and energy. Ability to focus on tasks for longer periods of time. Sleeping less. Prior to the trial my child would sleep 12hrs+ a night.		Energy Concentration Sleep Stamina

First effects of treatment in children aged 6–10 years at treatment start ***(Parents' response)***	**How soon?**	**Impact on**
Increased growth rate; Reduction in minor illnesses e.g. coughs colds; More energy; Improvement in walk test and stair climb assessments; Noticed within the first 3 months.	3–4 months	Energy Growth Illness Stair climb Walking
My son seemed less tired, particularly after school.		Fatigue
He was on an initial trial to study higher dosages of Vimizim. We saw (and he experienced) an immediate improvement in energy levels and ability to do things.	Immediate	Energy
The effects of treatment were not immediately apparent but over time I noticed she wasn't deteriorating as was expected. Her corneal clouding, to an extent improved, and she stopped wearing glasses. Stamina has vastly improved over the years. Treatment has definitely given her a new lease of life.		Eyesight Disease progression Stamina

First effects in children aged 11–15 years at treatment start ***(Parents/patients' response)***	**How soon?**	**Impact on**
(Patient's response) Upper body strength; My handwriting got better and still is; Feeling less tired; More energy in participating in schoolwork; Was able to sit for longer hours; Less pain; Breathe better; Could crawl faster than usual; Saw all these effects by the 2nd or third infusion.	One month	Breathing Energy Fatigue Mobility Pain Strength
(Patient's response) All effects were noticed around 4 weeks after starting. I first noticed that my eyesight improved - notably I could see the legs on a caterpillar which I had never seen before unless in photos. Sight was brighter, sharper, more vibrant. My energy and stamina increased allowing me to do more and achieve more. My pain levels decreased which also allowed more achievement. I noticed that my breathing became easier, lighter and I no longer snored - before treatment my chest was always tight and uncomfortable sometimes compromising my breathing capability. I was wheelchair dependent and struggled to weight bare before treatment but between 4 - 6 weeks after starting treatment I was able to mobilise myself and carry out any activity I needed or wanted to. Due to all the pain and invalidity I was mentally in a very low place, receiving the treatment and reducing my pain, increasing stamina and energy, and my sight, aided in increasing my positivity and my mental health.	One month	Breathing Energy Eyesight Mental health Mobility Pain Stamina
(Parents' response) Increased energy; Increased stamina; Pain reduction; Increased mobility; Increase in vision clarity! (At the age of 13 she saw the hairy legs on a caterpillar and the rings in a tree stump for the first time ever); All of the above were happening from about 4 weeks after starting treatment.	One month	Energy Eyesight Mobility Pain Stamina

First effects in patients aged 16–20 years at treatment start ***(Patients' response)***	**How soon?**	**Impact on**
Increased energy and motivation, better sleep and more comfortable mobility.		Energy Mobility Sleep
I cannot comment on when I first noticed the effects of Vimizim however overtime I have noticed that I can walk further distances, I feel stronger physically and my over health is better.		Strength Walking

First effects in patients aged 16–20 years at treatment start *(Patients' response)*	How soon?	Impact on
I experienced noticeable drastic physical improvements within 5 weeks of starting the treatment. These improvements have held consistent since I have started. I have significant muscular strength in my lower back and legs. This has enabled me to start walking and building off this strength I can now walk full time within the house. I have experienced no negative effects.	2 months	Walking Strength
I was quite used to not exerting myself because of fear of pain, and so didn't push myself too much. I was studying in university at the time I started treatment and the first things I noticed were not becoming breathless when walking from the bus stop to my classes. This was a huge improvement for me as previously I would be too exhausted to focus on the first part of all classes, but I could concentrate a lot better and also not be breathless. I also noticed less fatigue. I didn't feel debilitated at the end of the day, which was an everyday occurrence before starting treatment. I noticed this about 3 or 4 months after treatment started, when my endurance was tested as part of the trial and I tried to see if I could see the same improvements in my everyday life too.	3–4 months	Breathing Concentration Fatigue Pain Walking

First effects in patients aged 21–30 years at treatment start *(Patients' response)*	How soon?	Impact on
My sleep improved - I was sleeping less but I wasn't tired when I woke up so I think my quality of sleep had improved. Breathing - less laboured.		Breathing Fatigue Sleep
I have noticed I am a lot tired than I used to be. My strength has significantly improved especially in my hands.		Strength
More energy but also more tiredness. Travelling to clinical trial every week tired me out but I couldn't have done it without the drug helping me. My energy levels are more predictable; I don't suddenly run out of energy throughout the day. I can manage my recovery a lot better.		Energy Fatigue
I adapt quite quickly, so I can't remember a specific point of feeling any different. But after a few months I noticed that going to concerts, or other activities which would usually leave me tired and in pain for the next few days, was a lot less painful afterward, and for a much shorter time period (like a day). So essentially felt I could do more and not need as much time to recover.		Pain Recover
I noticed that my hair is growing faster and is healthier. I have more energy during the day and do not have to go back to bed as often.		Energy Hair
I noticed my teeth became whiter and stronger also my nails started growing and felt stronger. I noticed this within the first few weeks as before my teeth were always an off white/yellow and my nails would always break.	One month	Nails Teeth
Less tired, able to walk a bit more without getting tired. I have also noticed that I get unwell a lot less than I used to.		Fatigue Illness Walking

When I started, I noticed improvement straight away, I had two crutches and leg braces and my health was going downhill fast and probably would not be here if it was not for the Vimizim. Everything has improved, no longer need crutches, fitness, strength quality of life has improved, not been for any operations since on the drug or treatment injections since, my health is in the best condition considering my age.	One month	Strength

First effects in patients aged 31–40 years at treatment start (*Patients' response)*	**How soon?**	**Impact on**
Within 3-4 weeks.	3–4 weeks	
Not sure.		
I noticed my chest pains reduced significantly and I could sleep better at night.		Pain Sleep
After the first number of weeks, I began to notice a slight increase in my energy at work. I just wasn't quite as tired when I got home.	One month	Energy Fatigue
It was about a month of being on Vimizim that I started to notice anything positive. My breathing was a lot better; I didn't get out of breath as much as I did before, having a shower become easier. Pain had reduced a lot and become more manageable and I stopped taking my pain killer in August 2016. Had more energy could go out and not feel so tired. Stared to notice a lot of hair loss, hair is not growing at the same rate before starting Vimizim and now my hair is becoming very thin after about 4 or 5 months.	One month	Breathing Pain Fatigue Energy Adverse effect

First effects in patients aged 41–58 years at treatment start *(Patients' response)*	**How soon?**	**Impact on**
- The initial effects of treatment were gradual - I first started noticing them about two months after starting Vimizim. - I noticed an increase in energy levels and stamina and did not feel as lethargic. - I no longer had stiff joints and moving around was much easier - simple things like turning around in bed and getting up from a chair. - I also noticed a significant reduction in joint pain. Prior to Vimizim, I was taking ibuprofen on a daily basis for joint pain. At its worst, I could be bedridden for days with hip pain, and no pain relief would help. Within a couple of months of treatment, I was taking no pain relief as whenever I did experience any pain, I felt I had increased strength to tolerate it. It wasn't long before I stopped experiencing any pain. - My mobility improved - I was able to walk without holding on to things for support. My walking improved by 50% after 6 months. - My arms felt stronger and I was able to carry things like cups of tea or a plate of food.	2 months	Energy Mobility Pain Stamina Strength Walking

One of the first things I noticed was the reduced laxity of my wrists and I noticed this approximately 4 months after starting treatment. Previously I needed to use both hands to carry a mug of tea or a bottle of milk, and then realized I was able to use 1 hand as my wrists felt stronger and much less lax. Another surprise was that I could wring a cloth. Previously had to ask someone to do this for me but now I was able to this on my own. The reduced laxity was coupled with the strengthening of my hands, arms and upper core. I was able to climb stairs easier as my arms had the strength to pull my body up using the handrails. I could open the front door into our building which previously was too heavy for me and needed to rely on others to open. I could open jars, which previously, even if not tight still posed difficulties. Prior to starting this new treatment, I was experiencing pain in shoulders, wrists and neck yet these aches disappeared at the same time as the strengthening of upper core body. I also noticed I was experiencing less overall pain as well as increase in my energy levels.	3–4 months	Energy Joints Pain Stair climb Strength
Friends commented that than more energy before I started the programme.		Energy

EFFECTS OF TREATMENT OVER TIME

We asked: Have these effects of treatment continued, improved over time or are they no longer seen?

- The effects of treatment continued and/or improved over time, regardless of how long the patient had received the treatment for, or their age
- Patients who had missed an infusion or had to have a break for medical reasons noticed a deterioration, but immediately felt an improvement when back on treatment
- Some patients receiving elosulfase alfa for over 10 years could still see their health continuing to improve, with others feeling its continued benefit

Effects of treatment in patients who had received treatment for up to 2 years	Age (years)	Time on treatment	Effects of treatment
His energy levels and general happiness continued to increase for many weeks, it is hard to say how many. He is now a much happier child, with much more energy.	1–5	23 weeks	Continued Improved
Yes, they have improved a lot but when he misses 1 week of treatment it is noticeable, he is tired and slowing down.	1–5	1 year	Improved
Not sure.	1–5	1 year 1 month	Not sure
Yes the above effects continued and supported my child to be able to do more things she used not to be able to without pain and cry. The benefits she received from the treatment has brought great impact to her everyday life.	6–10	1–2 years	Continued
Improved over time.	31–40	1 year 7 months	Improved
Yes I feel this has continued.	21–30	2 years	Continued

Effects of treatment in patients who had received treatment for >2–5 years	Age (years)	Time on treatment	Effects of treatment
Continued.	1–5	2 years 2 months	Continued
The effects have stayed with me and have somewhat improved over time.	31–40	2 years 11 months	Continued Improved
Yes the effects are still there and I think the infusion has improved his overall health.	1–5	2.5– 3 years	Continued Improved
They have largely remained the same, though when it gets cold outside, I do tend to go back to bed to attempt to warm up some more.	21–30	3 years	Continued
About the same.	11–15	3 years	Continued
The effects have remained consistent. I haven't noticed them reduce or increase since starting the treatment.	21–30	3 years	Continued
The effects of the treatment have and continues to improve as I feel less tired and stronger.	21–30	3 years	Improved
Yes they have improved.	21–30	3 years	Improved
Stayed the same. In addition, I have had no chest infections or heavy colds.	≥41	3.5 years	Continued
Ever thing has stayed the same.	≥41	3.5 years	Continued
Continued as far as I can tell - still less pain/tiredness after big days out/activities. Again, it's gradual and I adapt quickly, so difficult to pinpoint anything specific, but looking back I feel an improvement.	21–30	3 years 7 months	Continued Improved

Effects of treatment in patients who had received treatment for >2–5 years	Age (years)	Time on treatment	Effects of treatment
These effects continued to improve for a couple of years and have since been maintained. These improvements are now my 'normal' state.	≥41	3 years 9 months	Continued Improved
They have continued, and while I started with more comfortable mobility (by which I mean less pain but no more/less active than I had been) I have now progressed to have greater mobility.	16–20	3 years 10 months	Continued Improved
Continues the same.	6–10	4 years	Continued
They have continued and improved with regular treatment. I had a six month period when I was not receiving treatment due to cannula access trouble (I had a port fitted which works beautifully) and within 1–2 weeks I had deteriorated and was at the pained, wheelchair-dependent state that I was previously in before treatment. Within 1–2 weeks of being back on the treatment the same effects were noted and continued to improve.	16–20	4 years	Continued Improved
They have all improved and continue to do so.	16–20	4 years	Continued Improved
Since I have started Vimizim, my energy levels have increased a lot. More focused at work and can take on great tasks. My breathing has become a lot less shallow. I used to be prone to getting the flu, since Vimizim, I only got it once. Did not last long, where as before, it would have taken weeks to clear up.	>31–40	4 years	Continued Improved
No longer seen.	>5–10	4 years	No longer seen
The benefits mentioned above are still very valid now and continue to enhance my life. These are the first physical benefits I noticed but more followed.	≥41	4 years 8 months	Continued Improved

Effects of treatment in patients who had received treatment for >5–<10 years	Age (years)	Time on treatment	Effects of treatment
The positive effects have continued. He, 7 years on, has not lost any mobility and shows brilliant stamina and energy. When he stopped compassionate treatment for 6 weeks during the fight last time for Vimizim he developed corneal clouding for the first time ever and his movement stiffened again. Within a few weeks of restarting his movement improved again, and four years on there has been no worsening of his corneal clouding. He also has less chest infections, and no longer needs grommets for his glue ear.	11–15	7 years	Continued
Yes - effects of the treatment have continued. He has the energy to take part in life. There is always a noticeable extra boost in his energy when his dosage gets increased (in line with his weight/growth).	11–15	7 years	Continued
Since she has grown up receiving the weekly infusion the condition has remained fairly mild and very stable. She enjoys taking part in all the things her peers do at school (other than active sport) and has the energy and ability to do so. She remains happy, healthy and mobile.	11–15	8 years	Continued
The improvements have continued.	11–15	8 years	Improved
These effects have improved significantly over the years. What started as my endurance increasing, has grown to me being able to build a life. The improvement has been incredible.	21–30	8 years	Improved
Yes. These effects have continued.	21–30	8 years	Continued
These effects have stabilised, I still do too much but now know when I'm getting close to my running out of energy.	21–30	8 years	Continued

Effects of treatment in patients who had received treatment for ≥10 years	Age (years)	Time on treatment	Effects of treatment
Still improving.	11–15	10 years	Improved
They improved over time and then reached a plateau. They can't combat every aspect of the long-term effects of the Morquio disease burden though.	11–15	10 years	Continued Improved
They have improved over time.	16–20	10 years	Improved
I just keeping improving and heavily relay on Vimizim for a better quality of life.	≥41	10 years	Improved
Growth continued for around 8 years then plateaued and became harder to measure accurately due to postural issues. Incidence of minor coughs and colds has remained low with no significant chest infections or similar Energy and stamina levels remained consistently positive until approximately 2 years ago when the structural effects of MPS IVA on the skeleton and airway began to become a limiting factor and as breathing becomes more of an effort, energy is reduced. Walk tests remained consistent for around 4 years and then declined a little over the next 4 years. During this time my child remained able to participate in physical activities such as swimming and drama and continued to have a useful ability to walk well over short distances. This has only changed over the last two years when the airway issues described above have become more limiting, along with the skeletal effects on his legs, with the knock-knees become much more extreme, which hinders walking.	16–20	10 years 7 months	Continued
Growth continued for around 9 years then plateaued as he neared the age of 17. This is in contrast with the expectation for individuals with MPS IVA who without treatment would usually expect to have stopped growing around the age of 8 or 9. The growth spurt he experienced at around age 14 was sufficient growth for the 8-plate leg straightening procedure carried out a few years previously to become effective and his legs are became and remain noticeably straighter, which improves mobility. Incidence of minor coughs and colds has remained low with only one significant chest infection over this time. Energy and stamina levels remained consistently positive until my child began to suffer pain from his hips at age 15 when the combined effects of the chronic pain and side effects of pain relief medication sapped his energy and reduced mobility. These hip problems were caused by the skeletal effects of MPS IVA and were resolved by successful bi-lateral hip replacement surgery 12–18 months after the onset of difficulties. This procedure would be unlikely to have been possible if he had not been on treatment as his general health, lung function and airway viability would be unlikely to have been well enough to withstand the procedure and make a good enough recovery. Following a period of recovery, his energy, stamina and mobility are better than ever. Walk tests remained consistent for around 4 years and then declined a little over the next 4 years. During this time my child remained able to participate in physical activities such as swimming and drama and continued to have a useful ability to walk well over short distances. This only changed during the onset of his hip problems and subsequent surgery and recovery when his mobility was extremely poor but recent tests have shown an improvement again.	16–20	10 years 7 months	Continued
The effects continue to be seen, mainly in mobility and stamina.	16–20	11 years	Continued

MAIN BENEFITS OF TREATMENT

We asked: What have been the main benefits of treatment to you/your child? Please be as specific as possible and give examples of the benefits you have noticed.

- The main benefits of treatment reported by parents of children under the age of 10 years were an increase in energy levels, less fatigue and an improvement in walking. These effects allowed the children to participate in every-day activities, such as nursery, physical play and playing with other children, which improved their quality of life
- Patients aged 10–20 years stated they had been able to go back to full-time schooling or college because of the treatment, with some children now being able to participate fully in school/college life, and in extra-curricular activities and sports
- Most patients aged 41 years and over reported an increase in energy, but in addition, an improvement in breathing
- From the age of 15 years, patients reported the effects of treatment contributed to their mental health, a benefit that became more prominent with age
- Patients also reported their colds and infections had been largely reduced, and suggested the positive effects of the treatment had given their body enough strength to have MPS IVA-related surgery

Benefits of treatment in children aged 1–5 years	**Time on treatment**	**Aspect**
More energy for him to use for playing, learning, and enjoying everyday activities more. He would never walk more than a few steps before, whereas now he is able to walk 200 meters without stopping on a good day. He is much brighter and more playful. Before he would get very tired after only a few minutes sometimes. A day in nursery used to render him completely immobile when he got home for the evening, even though he had an hours' sleep in the middle of the day at nursery. Now he is able to do a full day at nursery, with no sleep, and still has enough energy for physical play when he gets home.	23 weeks	Energy Fatigue Walking
Quality of life.	1 year	QoL
Level of energy increased; Can walk for longer; He is happier, plays with other kids.	2.5–3 years	Energy Mental Health Walking
More energy, hasn't deteriorated.	2 years 2 months	Disease progression Energy

Benefits of treatment in children aged >5–10 years	Time on treatment	Aspect
(1) Significant increase of energy level after my child received Vimizim treatment. She could not walk for more than 2 minutes and cried in pain and fatigue before starting treatment; after began the treatment she started to walk and move around more without complaint about her pain (she can play and study whole day without showing fatigue and is able to walk longer than 6 minutes). Example of improving fatigue was she used to came home at 3pm after school day and only laying down on the sofa but now she came home after 6pm (school day begins at 9am) and still be able to move around to play and study until bedtime about 9pm. (2) Significant change is her strength of big muscle movement such as jumping, skipping, climbing which she could not able to complete these movements before, but after the treatment she can, and she noticed her ability of doing these movement has been changed in positive way. (3) Noise from breathing and night-time sleeping disturbance episode was significantly reduced. (4) The cases of her upper-respiratory infections were reduced. She used to prone to chest infections very often and required antibiotics each time to settle. Since she began with Vimizim she only had light general cold infections. We would say her immune system has become stronger along with the treatment. (5) Physiologically my child became more confident in seeing herself is able to do more things rather than a disabled child. She can enjoy those things she used to struggle with such as climbing a playground frame (with adult supervision), participating in adjusted PE with one-to-one help, walking and moving around to get things with the support of a stool, able to do more tasks to self-care.	1–2 years	Breathing Energy Fatigue Independent Infections Mental Health Pain Sleep Strength Walking
Quality of life being able to be more physical without being in pain all the time No worries of catching chest infections continually.	4 years	Infections QoL Pain
More active and more energetic.	4 years	Energy

Benefits of treatment in children aged >10–15 years	Time on treatment	Aspect
Increased energy and stamina. He doesn't tire mentally at all. He shows no signs of physical exhaustion. His mobility is stable and has showed no deterioration over the seven years which is remarkable given Morquio is a progressive disease. He remains independent and does not have a wheelchair currently which is very unusual for a Morquio child of his age. The treatment has allowed him to fully participate in life - he is doing well at school, he has the energy to socialise and the independence and freedom to walk short distances home with his friends. His strength and flexibility is also stable which is vital for him to be independent. His hearing is normal and he has no grommets or hearing aids. His corneal clouding is slight and stable which causes him no problems. Vimizim has given him his freedom, his independence, it has given him the opportunity to be the best he can be because the debilitating effects of his condition are kept at a minimum, because of this drug.	7 years	Disease progression Energy Eyesight Hearing Independent Mobility Schooling Stamina Strength
Just that he isn't as tired as before, but seems to be slowing down recently as everything is more of an effort. This could also be due to his recent weight gain.	3 years	Disease progression Fatigue Weight

Benefits of treatment in children aged >10–15 years	Time on treatment	Aspect
No worsening of the condition. A great quality of life. Height - has continued to grow. Mobility - continues to walk Eager participant in school life.	8 years	Disease progression Growth Schooling Walking
More energy, continued growth and a huge reduction in clouding of corneas. My child is able to keep up with all her schoolwork.	8 years	Energy Eyesight Growth Schooling
More energy; No sleep apnoea; Less tired; Still able to walk; Improvement in his lung and walk tests at hospital.	10 years	Breathing Energy Fatigue Sleep Walking
Quality of life is great. No worsening of condition. Continued growth - now almost within lowest percentile for age group Happy with peers/friends. Nothing wrong with eyes/ears. Discharged from eye clinic. On 2 yearly check at audiology. Spinal curvature has lessened even with extra puberty growth. Eager participant in school life. Volunteers to help at school football. In national exam diet this year to do his Nat 5s. Quality life has improved for whole family - us the parents, his brother and sister. Vimizim has given everyone hope in the face of a tricky, potentially catastrophic condition which would worsen over time. Remains a very healthy, happy, active young man.	7 years	Disease progression Extra-curricular activities Eyesight Growth Hearing Mental Health Schooling
Ability to take part in main stream school, and after school activities such as drama classes, guides and swimming lessons. Some improvement of fine motor skills in addition to better stamina, so my child has been able to learn to play the guitar and enjoy making crafts.	10 years	Extra-curricular activities Fine motor skills Schooling Stamina

Benefits of treatment in patients aged >15–20 years	Time on treatment	Aspect
The most significant effect of being on treatment has been the delay to any deterioration and the limiting of the effects of deterioration, which are linked to the impact of MPS IVA on the skeleton which were already set in progress before starting treatment. For example, my child has been able to enjoy the majority of his primary and secondary school education alongside his peers, joining in with most activities with appropriate support and adjustment, he regularly cycled to primary school on an adapted trike and participated in annual amateur pantomimes and numerous other drama activities, regularly swam and joined a race running club.	10 years 7 months	Disease progression Extra-curricular activities Schooling
The most significant effect of being on treatment has been the delay to any deterioration and the limiting of the effects of deterioration, which are linked to the impact of MPS IVA on the skeleton which were already set in progress before starting treatment. For example, my child has been able to enjoy the majority of his primary and secondary school education alongside his peers, joining in with most activities with appropriate support and adjustment, he regularly cycled to primary school on an adapted trike and participated in annual amateur pantomimes and numerous other drama activities, regularly swam and joined race running and boccia clubs. A further benefit of the treatment is that it enabled my child to be well enough to undergo general anaesthetics and have hip replacement surgery.	10 years 7 months	Disease progression Extra-curricular activities Schooling Well enough for surgery
All effects were noticed around 4 weeks after starting. I first noticed that my eyesight improved - notably I could see the legs on a caterpillar which I had never seen before unless in photos. Sight was brighter, sharper, more vibrant. My energy and stamina increased allowing me to do more and achieve more. My pain levels decreased which also allowed more achievement. I noticed that my breathing became easier, lighter and I no longer snored - before treatment my chest was always tight and uncomfortable sometimes compromising my breathing capability. I was wheelchair dependent and struggled to weight bare before treatment but between 4 - 6 weeks after starting treatment I was able to mobilise myself and carry out any activity I needed or wanted to. Due to all the pain and invalidity I was mentally in a very low place, receiving the treatment and reducing my pain, increasing stamina and energy, and my sight, aided in increasing my positivity and my mental health.	4 years	Breathing Energy Eyesight Mental Health Mobility Pain Stamina
Pain reduction - regular pain relief is no longer required. Increased mobility - wheelchairs and stairlifts are no longer needed. Increased stamina a- able to complete a full day at college AND hold down an evening job 4 nights a week! Increased vision - no longer requires tinted glasses.	4 years	Eyesight Mobility Pain Schooling Stamina Work
I have progressed from walking short distances with a frame, to walking confidently with a frame, to now; I walk confidently with a stick and am able to walk longer distances unaided (in the house). I have found that I have had better sleep and therefore better concentration, drive and confidence, particularly academically, to the point that I am not studying at university. Growing more than usual and losing weight as a result of greater mobility and motivation has had an unfathomable impact on my confidence too.	3 years 10 months	Concentration Mental Health Mobility Schooling Sleep Walking Weight
I used to use an electric wheelchair but now longer use any mobility aids. I can walk further and I'm more mobile, allowing me to pursue the career I want to go into.	10 years	Mobility Walk Work

Benefits of treatment in patients aged >15–20 years	Time on treatment	Aspect
The main benefit is improved stamina and very little signs of physical deterioration of joints.	11 years	Disease progression Stamina

Benefits of treatment in patients aged >21–30 years	Time on treatment	Aspect
The most noticeable improvement I have experienced is the ability to walk again. Although I haven't noticed anything else besides this it is a massive step in my physical health.	3 years	Walking
The main benefits are that I am a lot more independent than I used to be. I can do a lot more for myself (for example personal care).	3 years	Independent
My breathing has definitely improved. I don't sound so chesty anymore especially when I do something the exerts me such as getting out of bed. Because of this I feel like I'm not needing to use my blue inhaler (salbutamol) as much as I would before starting Vimizim as I'm finding it easier to catch my breath. My joints don't feel so stiff anymore, I now find it easier to move off my armchair, I'm also not struggling to get out of my manual wheelchair anymore. I'm not as ill as often, especially of a winter. I would have a chest infection roughly 2 to 3 times yearly and I haven't had one.	2 years	Breathing Mobility Infections
During university, I managed to stop navigating around the university campus by bus and could walk around the campus with help of my wheeled book bag. I could do everyday things such as sit on the floor and get up independently. I can be a bit more independent with my living situation and make meals independently, bending to use an oven, whereas I was relying on support before Vimizim. I am no longer planning social outings by the distance of a venue from a bus stop or tube station, and visiting a supermarket no longer leaving me fatigued for the rest of the day. What may seem to the ordinary individual as normal day-to-day activities became my milestones and accomplishments. This is the effect that Vimizim had in my life. MPS did some damage to my body before I had started taking Vimizim, but having this improved endurance means that as i seek treatment for these conditions (arthritis), I am much more confident that I will be able to focus on recovery with lack of endurance no longer being a factor risking my recovery, like it had in the past.	8 years	Fatigue Independent Recovery Stamina Walking
I think the biggest thing is that I started the treatment after having hit a new low after university - I was physically and mentally drained, and part of me was worried about how feasible it would be to get a full-time job for me if I was going to be that tired all the time. Gotten better and better every year (and mental health improved) and have been in full-time employment since October. It's an ok level of tiredness, I'm not completely wiped out despite the long hours, and don't need to just sleep in my non-work hours but actually go out and be with friends as well. Part of this is the improvement of mental health, but that is very dependent on my physical state, which I think is helped largely by the treatment.	3 years 7 months	Fatigue Mental Health Work
Sleep; Breathing; Seems to have slowed down progression of symptoms Morquio.	8 years	Breathing Disease progression Sleep

Benefits of treatment in patients aged >21–30 years	Time on treatment	Aspect
I am more able to do everyday things without getting tired, this makes me happier as I am able to enjoy why I am doing and enjoy life. Before I started the treatment, if I went out one day the next day I'd have to stay home and relax as I'd usually be tired.	3 years	Fatigue Mental Health
Not having to go back to bed as often, if I do go back to bed it is because I am cold or in a lot of pain.	3 years	Fatigue
Predictable energy usage and recovery times. Increased exercise tolerance and stamina.	8 years	Energy Recovery Stamina

Benefits of treatment in patients aged >31–40 years	Time on treatment	Aspect
Vastly increased mobility. I have begun to walk unaided without crutches for the first time since I was 10 for short periods, with the duration and distance improving all the time. A significant increase in happiness and reduced depression and anxiety, and a massive reduction in the severity of pain. Weight loss due to increased mobility which has added to a slower resting heart rate. Enough energy to take care of myself properly- cooking healthier meals which also has improved my fitness and overall wellbeing.	1 year 7 months	Energy Mental Health Mobility Pain Walk Weight
I can sleep better at night and I am generally happier in myself. I do not feel as lethargic during the day as I did before treatment began.	2 years 11 months	Fatigue Mental Health Sleep
For me, the energy it has given me, as been extraordinary. I can work more efficiently and with more focus. I now have energy for my out of work interests.	4 years	Concentration Energy Leisure Time Work

Benefits of treatment in patients aged >41	Time on treatment	Aspect
Stronger fitter healthier my lung function has improved, skin has improved, walking improved, less worrying about the future as health improved massively.	10 years	Mental health Walking Strength Breathing Skin
Pain being reduced and not having to take any pain killers. Breathing easier and when getting out of breath it doesn't take as long to recover and carry on with what I am doing. Energy being able to enjoy life by going out not becoming too tired that I need to come home to rest.	3 years 6 months	Breathing Energy Fatigue Pain Recovery

Benefits of treatment in patients aged >41	Time on treatment	Aspect
- The increase in energy and lack of pain has helped me become much more active. I have managed to lose some much needed weight as a result - 13kg (over 25% of my body weight) - which has also improved my general health considerably. - I am able to walk further and stand for longer without my legs feeling weak and trembling. - Day to day tasks are no longer as tiring and I am able to get more done in a day. For example, I no longer need to rest after having a shower and getting dressed. - My lung function has improved. I no longer need to hold my head upwards to help keep my airways open. When talking, I no longer run out of breath and need to stop and take a deep breath before completing a sentence. I no longer breathe heavily. My speech is now clearer and louder. My sleep apnoea improved to the point where I stopped needing to use a CPAP machine to sleep after 20 months on Vimizim. I stopped snoring and no would no longer wake up in the middle of the night. I no longer feel sleepy during the day. Prior to Vimizim, I was prone to chest infections - every cold I had would develop into a full-blown chest infection that would require at least two weeks of antibiotics and I would be unable to get out of bed. Now, I only get a cold about once a year - they only last a couple of days and I have not had a single chest infection since starting treatment. I used to bring up phlegm every morning - I no longer do. - Prior to Vimizim, I suffered from "brain fog". I found it difficult to concentrate and to engage properly with other people. I could only concentrate for short periods at work and would often find myself falling asleep at meetings or at my desk. I couldn't concentrate on a film or play from beginning to end. Since starting Vimizim, the "brain fog" has cleared. Friends have commented on how I am much more engaged and sociable now. I no longer withdraw from conversations as I don't find talking and following conversations draining like I used to. I can sit through a whole film or play without falling asleep or losing concentration. I no longer fall asleep at work and can even tolerate working longer hours. - The time it takes me to recover from an activity is now much less. I now recover from a particularly busy day after a night's sleep, whereas prior to Vimizim, it could take days to recover from less activity. - I have noticed an increase in physical strength, particularly upper body strength. - The pressure in my eyes was high and I needed to take drops to prevent glaucoma. The pressure has now gone down to normal levels and I no longer need eye drops. - My skin has improved - I had very bad, sore acne which has now completely cleared.	3 years 9 months	Breathing Concentration Energy Eyesight Fatigue Infections Pain Recovery Skin Sleep Strength Walking Weight Work
From early on I started to notice benefits from this ERT. My upper core strength greatly improved and the laxity in my wrists reduced making everyday tasks much easier, such as carrying a mug of tea or opening a heavy door. This increase in strength meant that I could climb stairs using handrails more easily. Treatment also resulted in a decrease in pain and discomfort in my shoulders, wrists and neck. Sleep: Prior to Vimizim, I would feel tired after waking up and would struggle to get up. Now I seem to sleep much better. I feel much more energised, as I wake up refreshed and able get up without struggling. I also do not feel sleepy during the day as before. Energy: Compared to pre-Vimizim, I now have much more energy and stamina and suffer less fatigue. Previously I would have to plan my day in order not to wear myself out and the number of tasks and activities I could fit in one day were limited. After a shower, I would need to rest and lie down before being able to carry on with my day. Now I can shower, get dressed and get on with the rest of my day without needing to rest in between and complete more tasks in one day. This has had a huge impact on the quality of my life.	4 years 8 months	Breathing Energy Eyesight Fatigue Heart Illness Independent Mental Health Mobility Pain Recovery Skin Sleep Stairs climb

Benefits of treatment in patients aged >41	Time on treatment	Aspect
Mobility: Despite wearing knee braces on both legs and having arthritis in my hips, knees and ankles, I am able to walk further than before. My consultant has said that the 6MWT assessments have shown an increase in how far I can walk compared to my baseline without exerting myself. This has had a huge impact on my life as I can walk much further without needing to stop and rest continuously. Agility: I have become much more agile since starting Vimizim and family and friends have actually commented on this. I can stand up from a sitting position and get out of bed much easier than before and with much less stiffness in my limbs. I also notice that now I can transfer into and of the bath much easier and quicker than before. I use a mobility scooter and getting on and off as become easier. Pain: With Morquio comes pain especially in joints and having to take painkillers and other forms of pain relief. Prior to Vimizim I had to accept pain as part of my daily life and would adapt my day to what level of pain I was experiencing that day. This also meant I had to rely on painkillers. I suffered pain in my shoulders, neck, wrists and hands, as well as in my hips, knees and also ankles and that meant having to rest and stay at home more often. Since starting Vimizim I noticed my wrists are less lax, my arms and hands are stronger and I experience much less pain, to the point where I no longer require painkillers for them. The everyday stiffness and pain I use to experience in my hips, knees and ankles have been reduced. I have arthritis in my elbows, hips and knees and get flare ups of pain, but these have become less frequent and easier to tolerate and I recover more quickly. Without Vimizim I would probably have more frequent and longer lasting flare ups. Respiratory: I have had much less colds and no debilitating flu since starting Vimizim. Previous I knew that if I came into contact with anyone with a cold, I would also get it too, but I have noticed that this no longer the case. The amount of time it would take me to recuperate from a simple cold has greatly reduced. Prior to Vimizim, people would ask if I was ok as I was breathing heavily but I was not aware of doing so. Since Vimizim, I no longer breathe heavily and comments are no longer made. My respiratory consultant has said that my lung function has improved since starting Vimizim and it is illustrated by the lung function tests that are part of the assessments. Cardiology: Morquio causes heart issues. Since starting Vimizim my cardiac function has remained stable. Eyes: Cloudy corneas are a symptom of Morquio and which makes it difficult for ophthalmologists to see the back of my eyes. Since starting Vimizim, it has become easier to examine the back of my eyes. My vision has remained unchanged. Skin: Since my teenager years I have suffered from bad acne which continued into adulthood. No medical treatment helped, prescribed or otherwise. My skin was very sore and taut. Since starting Vimizim, my complexion has completely cleared, and my face is no longer sore and much more supple. Mental Health: All the above benefits of the treatment have affected my self-esteem as I feel much stronger and positive about myself. I do not feel constrained by my condition as I now have less pain, more energy, more mobility etc and do not have restrict myself. It has allowed me to be more independent and that is a huge boost for my self-esteem.		Stamina Strength
Stayed the same. In addition, I have had no chest infections or heavy colds.	3.5 years	Infections

SUSTAINED BENEFITS AFTER MORE THAN TWO YEARS OF TREATMENT

We asked: If you/your child have been on treatment or had received treatment for more than two years, what are the sustained benefits of treatment?

- Patients on treatment for over two years continued to receive benefits, regardless of how long they had been on treatment, or age
- The benefits were sustained even in those patients receiving treatment for over ten years

Sustained benefits of treatment in patients who had received treatment for >2–5 years	**Age (years)**	**Aspect**
More energetic; Can walk for longer; Does not get tired quickly.	1–5	Energy Fatigue Walking
Convenient as the nurses come to the home, in the comfort of the child's home.	1–5	Convenience
The pain management.	6–10	Pain
Again, not having to go back to bed as often, I feel that it has possibly improved my focus.	21–30	Concentration Fatigue
To stop the disease progressing.	11–15	Continued
They have continued and improved with regular treatment. I had a 6-month period when I was not receiving treatment due to cannula access trouble (I had a port fitted which works beautifully) and within 1–2 weeks I had deteriorated and was at the pained, wheelchair dependent state that I was previously in before treatment. Within 1–2 weeks of being back on the treatment the same effects were noted and continued to improve.	16–20	Continued
Same as previous question, Pain reduction - regular pain relief is no longer required. Increased mobility - wheelchairs and stairlifts are no longer needed. Increased stamina able to complete a full day at college AND hold down an evening job 4 nights a week! Increased vision - no longer requires tinted glasses.	16–20	College/work Mobility Pain Stamina Vision
The sustained benefits of the treatment are muscular strength.	21–30	Strength
One of the most sustained benefit is that I haven't had a chest infection since starting the treatment. Before starting Vimizim I used to get really bad chest infections (could be one after the other) in the winter months.	21–30	Infections
More energy, less pain.	21–30	Energy Pain
I am more able to do everyday things without getting tired, this makes me happier as I am able to enjoy why I am doing and enjoy life. Before I started the treatment, if I went out one day the next day I'd have to stay home and relax as I'd usually be tired.	21–30	Continued
My chest pains have reduced significantly and over time the involuntary lower-limb tremors I get have gone down.	31–40	Pain Tremors

Sustained benefits of treatment in patients who had received treatment for >2–5 years	Age (years)	Aspect
My energy levels are great; My immune system has improved; Sleeping better at night; Getting better at using the toilet; My breathing is better, less shallow and laboured; Less headaches; Mental health well-being is getting better.	31–40	Breathing Energy Illness Independence Mental health Sleep
Pain management; Breathing easier; Energy levels increased.	≥41	Breathing Energy Pain
- All the benefits mentioned in previous questions continue to be sustained. - I still have higher energy levels and stamina and have the energy to do more activities in one day. Day to day tasks do not drain me like they used to. I no longer fall asleep during the day. - Joint pain is virtually non-existent. On the rare occasion I do have joint pain, a low dose of ibuprofen is all I need for pain relief. I have had no episodes where I'm bedridden or where pain relief has been ineffective. - My lung function continues to benefit from treatment. I haven't had an asthma attack or chest infection since starting treatment. I sleep better and I continue to no longer need a CPAP machine to sleep. I breathe normally without needing to hold my head up. - I still have no "brain fog" or sleepiness during the day - I can concentrate for longer periods and I am more engaged in conversations. I can follow and enjoy a film or play from beginning to end without falling asleep or losing concentration. - My complexion continues to be clear and I have had no need to return to using eye drops to prevent glaucoma.	≥41	Breathing Concentration Continued Energy Eyesight Fatigue Illness Pain Skin Stamina
It has been 4 years and 8 months since I started Vimizim infusions (I started in May 2016) and all the benefits mentioned previously continue to be sustained.	≥41	Continued
Stayed the same. In addition, I have had no chest infections or heavy colds.	≥41	Continued
While they took a couple of years to take full effect (which may have been down to non-treatment-based variables, such as A-level stresses and port-a-cath surgeries), all the benefits I have mentioned have been sustained.	16–20	Continued
Just active.	6–10	Energy

Sustained benefits of treatment in patients who had received treatment for >5–<10 years	Age (years)	Aspect
For his condition not to deteriorate.	11–15	Disease progression
The sustained benefits have been described in questions above.	11–15	Continued
Sustained benefits - lack of progression of the condition and sustained energy and ability to take part in life.	11–15	Energy Disease progression
More energy, a happier less painful life and less clouding of corneas.	11–15	Energy Eyesight Mental health Pain
Less sleepy, better stamina. Maintaining the ability to walk.	11–15	Fatigue Stamina Walking
No worsening of the condition; Also the sustained, constant improvement in his energy levels mean he leads an active, fulfilling life; Still growing; Healthy - rarely gets sick. recovers quickly from colds.	11–15	Energy Growth Illness Recovery Disease progression
Better mobility; No decline in health.	16–20	Illness Mobility
The sustained benefit of increased endurance given by Vimizim is life-changing. I used to be a child without treatment, always forced to sit out of social events (such as birthday parties, play dates etc.) due to a lack of endurance and the fear of being exhausted, and now I am able to work full-time, getting involved in social events, both professionally and with friends and family. This is normality for some, but it was a pipe dream for me before Vimizim.	21–30	Fatigue Leisure time Stamina Work
Slowed down the progression of symptoms Morquio. My condition has remained stable since I started receiving the treatment, and given my age, I think without it, I would have deteriorated more.	21–30	Disease progression
Predictable energy usage and recovery times. Increased exercise tolerance and stamina.	21–30	Energy Recovery Stamina
Better quality of life, more independent, less of a burden on people.	≥41	Independence Qol

Sustained benefits of treatment in patients who had received treatment for ≥10 years	Age (years)	Aspect
The sustained benefits to treatment have been that my child has remained healthy and active. Any health issues relating to MPS IVA have been confined to distinct problems, in the main associated with skeletal problems that the treatment is not able to target. Being generally in overall good health means that where surgery could be considered an option to correct problems then my child will be well enough for this to be a realistic option. For example, in 2013 he underwent a successful cervical fusion with no health complications and new surgery is currently proposed for later this year to address the structural issues with his windpipe. This would not be possible without his overall health, lung function and stamina being as good as it is, which we believe to be due to the effect of continuing treatment. If the airway surgery is successful, this would make it easier and safer for further general anaesthetics to be carried out in the future which opens the door for further orthopaedic surgery to correct leg problems which would significantly improve the quality of his life.	16–20	Breathing Illness Stamina Well enough for surgery
The sustained benefits to treatment have been that my child has remained healthy and active. Any health issues relating to MPS IVA have been confined to distinct problems, in the main associated with skeletal problems that the treatment is not able to target. Being generally in overall good health means that where surgery could be considered an option to correct problems then my child has been well enough for this to be a realistic option. For example, the hip replacement surgery in 2017. This would not have been possible without his overall health, lung function and stamina being as good as they were, which we believe to be due to the effect of continuing treatment. This continued good health means that further surgery could be considered in the future if, for example, his cervical spine deteriorates, or the hip replacements begin to fail. A further sustained benefit has been the effect of growth continuing, every extra cm gained has increased the ease with which he can access his environment e.g. being able to reach door handles or the ability to see over worktops.	16–20	Breathing Growth Illness Stamina Well enough for surgery
Stamina	16–20	Stamina

IMPACT OF TREATMENT ON CHILD'S EDUCATION

We asked: Has being on treatment had any impact on your/your child's education? For example, have the number of hours or days attending education changed? Has the level of support in education changed? Has there been a change in ability to participate in extra-curricular activities? Please give specific examples.

- Most parents of patients under 18 reported that although, in the past, infusions were disruptive and had an impact on the number of hours their children attended education, this was resolved once infusions could take place at home or school
- Respondents of children under 18 reported their children spent more time in education after treatment as their levels of energy had increased, with children now being able to attend school full-time, and being able to partake in after school activities
- A large number of patients over 18 had attended/completed college or university. Schools and universities had always been accommodating of infusion days
- Some patients over 18 reported that treatment had played a key role in being able to complete their education as it had made them independent and had allowed them to be physically and mentally present for lessons

Impact of treatment on children 1–5 years old	**Impact on education**
He is currently attending nursery for 15 hours in total in a week. Infusion has not impacted his education	No impact
No as he started nursery this year and his day off from nursery is his treatment day	No impact
Yes hours of education decreased	Less hours
He is only 2 years old, in nursery, so is not part of formal education yet. However, it is clear that the extra energy has enabled him to develop in his speech and physical abilities as a much faster rate than he was able to before, as he was simply too tired most of the time. The nursery staff have noticed as great improvement in his ability to take part in all activities.	Able to participate Improvement Better speech Better mobility More energy

Impact of treatment on children 6–10 years old	**Impact on education**
Continues to have 1:1 in school to help with personal care however since treatment less days off and being able to participate in school as before treatment was tired all the time	Able to participate Less days off More energy
Before my child receiving her treatment at school, she did need to miss one day per week but this did not result in her fall in KS1 as the school has been support her learning with what she has missed in that day or adjusted PE to her treatment day so she wouldn't miss too much teachings. Now she has begun treatment at school for one year and we noticed that she is able to meet the requirement of school work and even performed exceeding in subjects she is interested in more. Physically she is able to participate a whole school from 9am–3pm without needing a rest or showing fatigue. She also attended 3 days after school sessions from 3–6pm and after came home still play and study up to 9pm. This wasn't possible before she started Vimizim treatment. Physiologically my child became more confident in seeing herself is able to do more things rather than a disabled child. She can enjoy those things she used to struggle with such as climbing a playground frame (with adult supervision), participating in adjusted PE with one-to-one help, walking and moving around to get things with the support of a stool, able to do more tasks to self-care at home and at school.	Able to do physical activities (e.g. PE) After school activities Confidence Hours improved More energy More hours Positive impact
None	No impact

Impact of treatment on children 11–18 years old	Impact on education
He is able to go 5 days a week now as I give him treatment at home. He was able to do his work experience recently where he was able to do full time work, without getting tired.	Full attendance More energy More hours Work experience
For the first 4 years of treatment he missed a day a week of school as his infusion was in hospital. We live 2 hours away, it was hugely disruptive, but completely worth it because of the benefits described above. He now has his infusions at school and does not miss lessons. He is fully participative in school - he can swim independently, he attends after school club two nights a week and goes home on his own on the school bus two nights a week as well, which means he has to walk and carry his bag from the bus stop home which is a 10 minute walk for him. He is thriving at school and manages all his lessons. This is so important. If he were to stop Vimizim now I think he would quickly be too tired to go to all lessons and certainly would have to stop coming home on his own and perhaps some of his after-school activities too. It doesn't bear thinking about.	After school activities Full attendance Positive impact More energy More hours
Less so as she has got older and now gets treatment at home. Only misses 4 classes a week and gets time set aside in her school timetable to catch up. She enjoys an active social life and has a lot of friends.	Active social life More hours Less hours
At school infusions now mean my child is not impacted hardly at all. In the past a day in hospital wasn't easy but it's much better now.	Full attendance No impact
Yes, a lot of school was missed, and he is not top of his year. Being a boy, I think he is less interested in school and pushing himself.	Less hours
The early stages of treatment during the trial period meant missing vast amounts of schooling. We now home infuse, so can work around school, and my child is able to attend full time, rather than missing a day a week. The level of support at school has not changed, but they are able to take part in more activities, e.g. the school play, singing club, guitar club.	Full attendance More hours
During the early stages of treatment, which were part of the clinical trial, one day a week of school was missed to attend the hospital for treatment. However, the increase in stamina as a result of treatment meant that it was possible to catch up work and minimise the impact as far as possible, with support from the hospital teaching service. Once the trial process had concluded and the option to carry out infusions in school was available then this was taken advantage of and school attendance went back to 5 days a week. It is highly likely that without the positive benefits of treatment then reducing stamina would have led to his school timetable being reduced to accommodate rest breaks or rest days at home. It was only in the last 6 months of his GCSE year that the airway complications meant that being in school 5 days a week became too much. Even then, with appropriate support in place he was able to complete his studies, sit the exams and get a good set of GCSE results. It is also worth noting that over the course of his education he had a minimal amount of time off school for illness, with a continued absence of chest infections, tummy bugs etc	Full attendance More hours More energy Achieved GCSEs
No	No impact

Impact of treatment on children 11–18 years old	Impact on education
He volunteers to help at school football and goes to Explorer Scouts. He is in his first exam year at High School. (S4 - and studying for Nat 5s). He has missed a lot of school particularly when we travelled to Manchester to take part in the trial but he is working very hard this year to catch up and make sure there are no gaps in his knowledge. He attends extra study session put on by the school and has a home tutor to help him with English. Now with his infusion done at home the time out of school is much more limited and he only misses the PE sessions in the timetable. He has an English tutor.	Able to do physical activities After school activities More hours Less hours Extra tuition
Yes. Before treatment I could not complete more than an hour or two at school for being in constant pain and discomfort with no energy to get through the day, whereas now I drive myself to college, complete a full day and then drive myself to work four a 6 to 8 hour shift 4 days a week, all without any walking aids or assistance, no wheelchair and very little pain relief. In school I had a 1 to 1 assistant which I no longer need.	Able to drive Full attendance to college Independence Less pain More energy Part-time job while studying
Before treatment she could only manage a couple of hours a day for 3–4 days a week in school. She now attends college full time and holds down an evening job 4 nights a week	Full attendance to college Part-time job while studying

Impact of treatment on patients 19–30 years old	Impact on education
I left full time education a number of years before I started on the infusion, but I did end up dropping an Open University course, because I still struggle with exams.	Struggled with exams (disease)
While I was at school I missed one day a week, however this did not impact my ability to get into college, which allowed me to have my infusion on the weekly study day, now at uni I have my infusions on one of my days off and the uni have worked well around missed placement with top up days.	Attends university Infusion on time off Placements
Treatment has hugely impacted on school/college attendance in the past. Both school and college were excellent at providing extra help/reducing GCSE subjects etc However my daughter's determination to prove she was as capable as her peers also showed. Now she is at University, and they too are excellent at allowing time off for infusions and hospital visits. There have been occasions where days/weeks of work placements have had to be extended in order to meet the course criteria, but this has been achievable. I.e. because of missing a day-a-week for infusions, time had to be made up.	Attends university Huge impact on attendance in the past Infusions on time off Placements
Completed my education by starting university full time, didn't need any time off and didn't have any major illnesses.	Completed university No issues

Impact of treatment on patients 19–30 years old	Impact on education
At school, before Vimizim, I did OK at school. I got a mix of As, Bs and Cs for my GCSEs and Bs and Cs for my A-levels. Navigating around school often left me exhausted and I would find full school days quite debilitating. I had to miss some days when I wasn't physically up to facing a day in school. I started Vimizim at university and honestly owe it my education. I graduated from a reputable London university with a first class with honours in Computer Science BSc. I was able to attend many more classes and be fully physically and mentally present for the lessons than I ever was in school. I missed less days due to pain and socialised with my peers better than I ever had at university.	Completed university Less pain Mentally present More attendance More energy Owes education to Vimizim Social life
When I was at university, I had to complete practice placements. I had to complete my final placement part time to allow for my treatment and the extra study day that I had to put in to achieve my degree.	Completed university Placements
I am in a position where I will be recommencing British Sign Language lessons and returning to university in September to complete my further education that I abandoned 15 years ago due to poor health.	Better health Returning to university
None.	No impact
I took work to hospital for the first 12 treatments and while studying my GSCE's I had treatment later in the afternoon to minimize lost school time. Because of this we were able to make my education work around treatments. In addition to this, the increased motivation and concentration more than made up for any lost time. While on treatment, I have completed my GSCE's and A-Levels to a decent degree, captained a three-times winning disability sports team and have pushed my hobby to the limits on TV's LEGO Masters. As such I can confidently say that the MAA has only had positive effects on my education and extra curriculum activities.	Able to do sports activities Achieved GCSEs & A-levels Extra-curricular Positive effects on education

IMPACT OF TREATMENT ON EMPLOYMENT

We asked: Has being on treatment had any impact on your/your child's employment? For example, has your/their ability to work changed? Have the number of hours or days attending work changed? Has the level of support in work changed? Please give specific examples.

- Patients reported being able to work after starting treatment, with some of them balancing part-time work and college, and some now able to work full-time without being exhausted
- Some patients that had to leave work before starting on treatment had been able to return to paid/unpaid work
- Most working parents of children on treatment were able to reduce the number of hours they worked to fit around their child's treatment. For others, their company accommodated flexible working, including working from home on infusion days
- A few mothers had initially stopped working but had returned to work part-time thereafter
- One mother stated the improvements in their child after receiving treatment, had benefited her ability to work as the child is now attending school full-time

Impact of treatment on patients' employment	**Age (Years)**	**Impact on employment**
Before treatment I could not complete more than an hour or two at school for being in constant pain and discomfort with no energy to get through the day, whereas now I drive myself to college, complete a full day and then drive myself to work four a 6 to 8 hour shift 4 days a week, all without any walking aids or assistance, no wheelchair and very little pain relief. In school I had a 1 to 1 assistant which I no longer need.	16–20	Now able to work part-time while at college
Now able to work 4 nights a week after college.	16–20	Now able to work part-time while at college
YES. Able to work full hours and not feel completely wiped. And work has been very accommodating, giving me a room to have the nurse start the treatment, and then I've been trained to finish it by myself, so I can just go back to regular work after that first hour.	21–30	Full-time work Accommodating for infusion
I did not have Vimizim from about 2 months before I started employment to about a year into it as I was between the trial and the compassionate use programme. In the beginning, I was doing well with settling into the working world, but I noticed a decline in my endurance. I found myself having to turn down work related lunches and outings, as locations could sometimes be a bit too far for me to walk from the office building. I was increasingly unable to lift small loads, and became short of breath whilst walking small stretches, such as carrying a laptop to a meeting room. These were milestones I had reached whilst on the enzyme replacement therapy trial, but after a short break, I found myself held back from reaching them. Having been on Vimizim for the past 5 years, I have noticed the effect that having more endurance has had on my professional life. I am able to socialise a lot more at work than I did in the beginning, I have worked extra overtime as I don't find myself exhausted by the end of the day. All these factors have led to me seeing multiple promotions and nominations for industry awards.	21–30	Able to work extra-time as not exhausted More endurance Now able to attend work-related socials Promotions and awards

Impact of treatment on patients' employment	Age (Years)	Impact on employment
I currently work 22.5 hours a week whereas I used to work full-time. I feel I could work up to 30 hours with one day off for my infusion. It has been suggested that I could have my treatment at the workplace, but as the infusion makes me feel tired, I don't feel able to work at the same time as having my infusion.	21–30	From full-time to part-time Tired after infusion
I resigned from paid employment 2 years ago before receiving Vimizim. Since my health has improved, I have been able to contribute to much more meaningful voluntary work. This ranges from political canvassing (I have been encouraged to run as a town councillor which I am considering), I have signed up to volunteer as a counsellor for Childline, and I am active in a homeless outreach campaign where members sleep rough over the Christmas period, while working in soup kitchens and other food distribution sites during the days. None of which I would manage without the increased and improving levels of mobility and physical fitness I am now able to enjoy.	31–40	Left work before treatment Now able to undertake active volunteer work due to improved mobility and fitness
I have more energy to do my work now.	31–40	Improvement
- I continue to work as a software engineer for the same employer, but my working practice has changed since starting treatment. - Prior to Vimizim, I was working full time, 5 days a week, working from home when necessary. My commute took one hour each way. I'd find work completely draining as it would use up all of my energy and I had virtually no life outside of work. Monday to Friday, I would go home directly from work, have dinner and go straight to bed = I was too exhausted to do anything else. I'd spend weekends recovering from the week at work. I would take a lot of time off sick, mainly for joint pain, exhaustion and chest infections. I was considering reducing my working hours significantly as I felt I was no longer able to continue to work full time, but I put this decision on hold when Vimizim became available to me. - Since starting treatment, my ability to concentrate and work for longer hours has improved, and as such my productivity has increased. I can now do a full day's work without feeling drained. I rarely need to take time off sick. I now have more energy to be active outside of work, so I have changed my working practices to make the most of this energy and improve my life/work balance. I now work from home and a couple of months ago, I reduced my hours by just half a day a week. Vimizim has allowed me to enjoy life outside work - I still have energy to enjoy leisure time after work and at weekends.	≥41	Energy levels have improved and now has a work-life balance Can work for longer hours without getting tired Productivity has increased No time off sick
I worked for my father, who was a sole trader, for many years but it was from home and at my own time. He has reduced work and retired so I am no longer in employment.	≥41	Used to work from home Not working
I retired six months after starting treatment. I found balancing the two difficult and now think it was unsustainable due to the number of failed cannulations.	≥41	Could not balance work-treatment Stopped working

Impact of treatment on parents' employment	Impact on employment
Yes I had to change my job role to work around my child I had a lot of support from my parents, hospital and MPS society.	Job change
No.	No impact
My work are flexible and allow me to work from home on her treatment days.	Flexible Work from home on infusion day
I do not work outside of the house, I am attempting to write a novel, so on any day apart from a Monday (when I do the treatment) I am working on my laptop.	No impact
I stopped working when she got on the drugs trial. I now work part time in another job and work from home on her infusion day.	Stopped working but now part-time Work from home on infusion day
As being on treatment has made my child healthier and have more energy and stamina then knowing that they are on the whole able to be in school full time has made it possible for me to plan when I am able to work. Obviously being part of the clinical trial was a big commitment and impacted on my ability to work, but once infusions switched to taking place in school then I was able to return to part time work. Having observed the recent difficulties faced by my child in attending school full time (and the subsequent impact on my ability to go to work) during the final stages of GCSE, due to his airway complications, this highlights that without treatment this level of disruption is likely to have been in issue for much of his education. The associated uncertainty around whether or not he could attend school on any given day would have made it impossible for me to work at all.	Child's improvement has benefited parent's ability to work Stopped working but now part-time
I stopped working to make sure we could get him (and his sister) to Manchester every week for the drugs trial. I now work part time in a different job and work from home on their infusion day.	Stopped working but now part-time Work from home on infusion day
I've had 2 jobs, one in a nursery and one as a TA in a special needs school. Both jobs have been accommodating to my needs.	Jobs were accommodating

IMPACT OF TREATMENT ON LEISURE TIME

We asked: Has being on treatment had any impact on your/your child's leisure time? Please give specific examples of any impacts on your or your child's time outside of school or work and at weekends.

- The positive impact on patients' leisure time was evident across all ages
- In children under 18, increased energy meant they were now able to socialise with their peers, undertake outdoor activities, attend after school activities and even participate in sports
- Infusions had not affected leisure time in children, with some finding ways to interact with their friends, remotely, while receiving the infusion
- In patients over 18, the effects of treatment also improved their social life, their ability to travel independently and to undertake new hobbies

Impact of treatment on patients' leisure time	Age (Years)	Impact on leisure time
Yes, he is now able to play for longer, and to enjoy it far more as he has enough energy to keep up with some of his peers for longer than he used to. He still does not have as much energy as a typical 2 your old but is much closer to typical than he used to be prior to treatment.	1–5	Keeps up with peers More energy Plays for longer
No impact.	1–5	Leisure time not affected
We encourage her to do what other children her age do within reason.	1–5	Leisure time not affected
No.	1–5	Leisure time not affected
Gaining more energy and strength in her body helped my child to develop more outdoor leisure opportunities. She did not have any outside school activities before, now she joined an after-school club for 3 days per week, a choir class once a week, and a swimming lesson once a week. She never was able to join any before due to lack of energy and strength. We also arrange family short trip during school holiday, and she is able to move around with balance bike and scooter. She is also able to play facility in a children playground such as climbing frame, swing, slide, balance wood.	6–10	After school activities More energy Outdoor activities Riding toys/park Short trips
More play time more energy positive impacts only.	6–10	More energy More play time
None.	6–10	Leisure time not affected
Having infusions at school and home has an impact on leisure time e.g. missing breaks, not being able to see friends, but the cost is worth it for the benefits he gets. Because of Vimizim He has the energy and physical ability to participate in leisure activities in the daytime such a laser quest, and things in an evening where otherwise after a busy day he would be too tired to attend or enjoy it.	11–15	Evening activities Lees free time at school More energy Physical activities

Impact of treatment on patients' leisure time	Age (Years)	Impact on leisure time
No.	11–15	Leisure time not affected
Not really - she accepts it is a weekly treatment and she has plenty of free time to see her friends.	11–15	Leisure time not affected
My child can now socialise out of school now she's on treatment as she's not as tired.	11–15	More energy Socialising
Not really. The Xbox is always accessible	11–15	Leisure time not affected
My child is able to spend more time doing things they enjoy at weekends, rather than spending all the time in bed recuperating from the week.	11–15	Able to do more leisure activities
Not really - he gets his treatment from 2–8pm every Wednesday - he has plenty time to see his friends at the weekend and other nights after school. He is very accepting that this is his routine and still plays with friends on Xbox when he is having his treatment.	11–15	Leisure time not affected Plays with friend remotely while receiving infusion
Throughout the majority of the ten years my child has been on treatment he has continued to be able to take part in a range of after school and leisure activities. He attended a weekly after school drama class throughout his primary and secondary school time and had weekly swimming lessons. He also took part in an amateur pantomime every year, which required a lot of energy and stamina. He was able to attend weekly rehearsals for several months of the year and coped with an intensive week of performances. Whilst he was tired the next day and needed time to recover, one day's rest was sufficient to get back to normal, whereas without treatment we would have expected him to need several days or a week. Without treatment he would have been unlikely to have the energy and stamina required for after school and weekend activities.	16–20	Energetic after school activities Leisure time not affected More energy Sports
I now have the energy and stamina to go out and socialise with my friends, which I was unable to do before.	16–20	Socialising
He attended a weekly after school drama class throughout his primary and secondary school time and had weekly swimming lessons. He also took part in an amateur pantomime every year, which required a lot of energy and stamina. He was able to attend weekly rehearsals for several months of the year and coped with an intensive week of performances. Whilst he was tired the next day and needed time to recover, one day's rest was sufficient to get back to normal, whereas without treatment we would have expected him to need several days or a week. Without treatment he would have been unlikely to have the energy and stamina required for after school and weekend activities. In the last three years he has pursued competitive opportunities in the sport of boccia, training once a week and regularly traveling around the country for matches. This is a very tiring experience but due to the benefits of Vimizim treatment he is well able to manage his stamina levels and recover rapidly the next day. He has also taken up the sport of race running, again pursuing competitive opportunities. This would be significantly more difficult for him without the benefits of treatment.	16–20	Competitive sports Energetic after school activities Leisure time not affected More energy Travelling
No, infusions are worked around education/social/recreational activities so there is no impact to day to day life.	16–20	Leisure time not affected

Impact of treatment on patients' leisure time	Age (Years)	Impact on leisure time
In the summer (2019) I began taking myself swimming, something I find I can do easier in recent years. This stopped over winter, though I hope to resume it in spring this year (2020). Been able to push myself physically and build upon the positive work the treatment has had to my mobility is something I am glad to finally be able to do.	16–20	Increased mobility Sports
I have more energy to do things now.	16–20	More energy to do things
On occasion yes, but generally my daughter's friends make allowances and arrange to meet when my daughter is free.	16–20	Rarely
Was able to meet with friends and stay out longer**.**	21–30	Socialising
Weekends used to be a time to recover from the effects of having a debilitating condition during a busy week, but now there is room for socialising more, including travelling for brunch with friends. I still need some time to recover (as I'm sure do most people!), but the time that I used to spend lying down and watching tv whilst recovering, can now be used for what i want to do, whether that's seeing friends, swimming at my local pool, or still lying down and watching tv - it is my choice and not because I am unable to do anything else.	21–30	Now has a choice Socialising Sports Travel further
Again, answered above - big thing is that I don't feel like I have to choose between work and leisure, I can do a healthy balance of both without sacrificing too much of either one because I have the energy to, and don't feel as much pain for going for longer periods of time without rest.	21–30	Now has a choice
No. I am always tired after I've had my infusion, so I don't plan to do anything on those evenings. If I have a leisure activity to go to on infusion days, I usually try to change my infusion to another day.	21–30	Tired after infusion
It has impacted positively on leisure time. I am able to travel much farther distances without joint pain and have been able to revive friendships with friends and family all over the country. I have begun to collaborate with local musicians again and will occasionally perform live- something prior to Vimizim I hadn't done in a musical setting for a decade.	31–40	Music performances Socialising Travel further
I am no longer as tired and can enjoy myself to a fuller extent.	31–40	More energy
No.	31–40	Leisure time not affected
Able to do more activity and be more independent.	≥41	More activities Independent

Impact of treatment on patients' leisure time	Age (Years)	Impact on leisure time
- Treatment has had a significant impact on my leisure time. I now have more energy to enjoy any spare time I have outside of work. I've become more sociable with friends. I can do my own shopping without relying on family members to do it for me. I visit museums and art galleries more often, I go to the cinema, to concerts and to the theatre more often. I have become an avid reader as I no longer find reading tiring. - I have also taken an interest in learning new skills. I have started to take regular short course in ceramics and have made a selection of mini pots. I am now looking into taking this further by doing a longer course. I have started to learn British Sign Language. After a recent trip to Berlin, I've started to learn German too. I'm now also looking into learning how to play a musical instrument. I wouldn't have considered any of this prior to Vimizim - I wouldn't have had the energy. - I'm also spending more time engaging with family.	≥41	Able to read again Learning new skills (e.g. pottery, instrument, German) More energy More time with family Own shopping Socialising Visit museums, cinema, etc
Since starting Vimizim, I have been able to enjoy my leisure time much more. Prior to treatment, I rarely went out as I had no energy and a lack of confidence to do things on my own. I often declined invitations as I would be too tired or in too much pain or that I knew that I would have to leave early which would be humiliating. Since Vimizim, I now have more energy and more confidence to go out and meet up with people. I started to go to the theatre and cinema and will now go to my local park to read on my own, which is something I would not have considered possible. I find it easier to engage with people as I feel more positive about myself.	≥41	Engaging with people Independent trips to park More energy More confidence Socialising Visit museums, cinema, etc
I write Thursdays off for the treatment with Friday as back up if fail to be cannulated.	≥41	Less time

Impact of treatment on parents' leisure time	Impact on leisure time
I have more time off.	More time off

IMPACT OF TREATMENT ON INDEPENDENCE

We asked: *Has being on treatment had any impact on your/your child's independence? Please give specific examples.*

- Independence had improved across all ages
- This was most noticeable in patients aged 15–19 years, with these patients reporting they had been able to undertake household chores, pass their driving test, prepare meals and travel independently
- Some patients reported treatment had not had any impact on their independence
- Adult patients stated an increase in independence had meant more socialising and going out, and were now able to travel by themselves and do their own shopping

Impact of treatment on patients' independence	Age (years)	Impact on independence
Gaining more energy and strength in her body helped my child to develop her self-care ability such as brushing her teeth, washing her face, get dressed, putting socks and shoes on. These actions were very difficult to complete due to her hypermobility. Now she can complete them independently most of the time. Another example is she loves reading books, now she is able to complete the actions of choosing books, touching screen to borrow and return books in a library (with height support chair). This is evidence showing that she has more strength on her arms and hands to carry more things and complete more tasks. My child explored that she can do more now, so she enjoys to try new things she used not to dare to try or lack of confidence to do.	6–10	Improved: Carries more things Managing borrowing books/library More confident Self-care
No.	6–10	No impact
Has independence has increased dramatically	11–15	Improved
I carry out the infusion and during that time my son is extremely lethargic and needs every doing for him, including carrying him to the toilet.	11–15	Dependent during/after infusion
It has had a positive impact - She likes to do everything for herself and is of an age where her friends are all starting to go out. She regularly goes out on her bike with them. Without her weekly treatment she would not have the energy to do this.	11–15	Improved: Can go out with friends by herself by using her bike
Given her more independence in a way as she is more alert and awake in herself.	11–15	Improved
Not really.	11–15	No impact
He has become very independent over the last 2 years and goes everywhere on his bike. To and from school, the barbers, the shops, the dentist all by himself. He carries his onto the train if he and his friends are going into town or further afield. Had he not been receiving Vimizim regularly I am very doubtful he would have the energy, inclination or ability to do this.	11–15	Improved: Travels independently using his bike
Having been on treatment, my child is able to independently get washed and dressed and carry out daily activities around the house. Until the last year where his airway complications have become a bigger problem, he would prepare drinks and snacks for himself and was developing a greater level of independence. He is anticipating continuing the path towards greater independence following the airway surgery later this year.	16–20	Improved: Self-care Meal preparation

Impact of treatment on patients' independence	Age (years)	Impact on independence
At age 18 my son is seeking to develop increased independence at every opportunity. As his stamina and mobility have improved significantly following his hip replacements, he is learning to carry out simple food preparation and can easily prepare drinks and snacks. He moves around completely independently in the house and washes and dresses independently. He has recently passed his driving test and has his own wheelchair adapted vehicle. All of this would be significantly more challenging if he was not on treatment due to the benefits of his increased general health, stamina and mobility and that fact that this good health enabled him to have the hip surgery to restore his mobility.	16–20	Improved: Driving test Meal preparation Self-care
A massive improvement on my independence.	16–20	Improved
It has had a massive effect on independence - the main thing being that did to increased mobility, stamina and pain reduction she has been able to learn to drive a normal automatic car with no adaptations which means she can take herself from home to college and to work and she is now able to socialise independently We infuse independently at home with myself (mother) administering the drug which has had an even better impact on home life as we are not dependent on nurse involvement.	16–20	Improved: Driving test Socialise independently Travel to/from school alone
I still use a powered wheelchair outside of the house, something no amount of treatment will change, but the increased mobility in the house has greatly increased my independence. I feel comfortable that I can stand on my footplates to reach something from a cupboard whereas before I was worried my legs could give way. I can confidently answer the door (something significant given that I study from home) whereas before my use of a walking frame (not stick) and shorter stature from what I am now made me feel vulnerable. Confidence (likely brought about by the visible changes caused by the treatment like increased stature and weight loss) has lead me to travel further independently, for university trial days I visited Sheffield regularly, and more recently I traveled to Newcastle for a LEGO show with a group I am now a part of.	16–20	Improved: Answer the door Independent travel Reach objects in cupboards
I am completely independent.	16–20	Independent
Not at all.	16–20	No impact
Was able to write my own notes and never needed a scribe for lessons and exam time.	21–30	Improved: Independent at school
Yes, I am more independent since starting treatment as I find I can do a lot more for myself now.	21–30	Improved
I don't think so, I still live with my parents.	21–30	No impact
I was already an adult and living independently. Will say that I'm more likely to go out though, even for small things like going to the shop because I want something - before I'd often feel too tired if I was already inside.	21–30	Improved: More likely to go out Own shopping
No.	21–30	No impact

Impact of treatment on patients' independence	Age (years)	Impact on independence
Before I started Vimizim and was considering university, my independence was limited. I struggled to do small things like change my own bedding as it would take me a long time. As my family and I reside in London, I had to think carefully about my future plans. Physical disability did not affect my ambitions; it did however restrict my options. Since I was not physically independent enough to move away from my support network, I studied BSc in Computer Science at a reputable London university. During university and many months after I had started Vimizim, I decided to try living independently in the university halls of residence as I had seen an improvement in myself. I was able to live alone and make the majority of my own meals. I was still nearby home and so when I needed extra assistance, it was never far away, but I could be independent a lot more than I thought I was able to, and ever was at home. As many graduates in London do, I live with my family at the moment. I help around the house as much as I can. I can stand long enough to do the dishes and do my own laundry, but I avoid anything which means I will have to carry heavy loads such as vacuuming and mopping. I would say I can think about an ambition to live independently in the future, still close to my family in case I need assistance, but with Vimizim, I see London property prices more of a barrier to this than my physical condition!	21–30	Improved: Meal preparation House chores Lived alone at university
It has allowed me to rely much less on other people. I look forward to needing to pop to the shops, rather than asking someone to go for me. or wait until they are leaving. I am much more motivated to maintain good fitness levels. If I have done fewer than 10k steps I will push myself to do some extra cardio-vascular exercise as the obstructions that prevent me from doing so are no longer physical thanks to Vimizim.	31–40	Improved: Mobility Own shopping
I am more outgoing and can hold a conversation.	31–40	Improved More outgoing
Before if going anywhere would need someone with me to help, now I can attend events or hospital appointments independently.	≥41	Improved: Mobility Own travelling
- I have always been a staunch defender of my independence, so I think the biggest change here has been that I am now able to go out and do my own shopping, which I didn't have the energy to do before. I no longer have to rely on anyone to do that for me.	≥41	Improved: Mobility Own shopping
Vimizim has certainly given me much more independence as it has improved my health all round. My energy has increased allowing me to participate more at home with my family as well as do things for myself e.g. I relied on others for shopping but now able to go on my own (albeit using a mobility scooter) I can go out independently as I now feel stronger and more confident. Vimizim has given me not only benefits in health but also in self-esteem.	≥41	Improved: Participate with family Mobility Own shopping Go outside by himself
No.	≥41	No impact

DISADVANTAGES OR PROBLEMS WITH TREATMENT

We asked: Please tell us about any disadvantages or problems you have had with treatment

- The main disadvantages for families of patients on treatment were not being able to take long holidays, scheduling around infusion days and infusions being time consuming
- A large number of patients and parents/caregivers said there were no problems or disadvantages with the treatment
- A few logistics problems had been encountered with the home delivery of elosulfase alfa and the availability of nurses
- Other reported issues included unsuitable veins, tiredness post-infusion and minor reactions
- Some patients said all these disadvantages are outweighed by the benefits of the treatment

Disadvantages or problems for the child with treatment	Patient/ Family	Disadvantages
For my wife and I it has meant a weekly trip to Manchester, and therefore taking time off work. That's the only ill effect, and my work are very understanding, allowing time off as necessary. It is also harder to travel now that he needs weekly treatments. Other than that, no disadvantages.	Family	Time off work Holidays
You cannot go away on holiday for more than 6 days as missed treatment is not good for my child.	Family	Holidays
None.	Patient/ Family	None
None.	Patient/ Family	None
Too time consuming.	Family	Time consuming
No.	Patient/ Family	None
Makes child tired after infusion.	Patient	Tiredness
Very few problems. Now He has a port and his treatment is at home and school it is minimally invasive and upsetting for him. It is part of his weekly routine.	Patient	Few
He has never had a reaction to treatment and has learnt to overcome his fear of cannulation over the years of getting this treatment. I honestly can't think of a downside.	Patient	None
None.	Patient/ Family	None
Problems were psychologically and physically. Not liking needles, not understanding why he has had to have the infusion. All he wanted was to be normal like his friends, and unfortunately, that wasn't something either I or Vimizim could guarantee.	Patient	Psychological Physical
It takes about 6 hours a week to complete the treatment, which is draining after so long on treatment. My child has experienced some mild reactions to the treatment in the past such as rashes, and high temperatures.	Patient/ Family	Time consuming Mild reactions

Disadvantages or problems for the child with treatment	Patient/ Family	Disadvantages
Our experience has been that the benefits of treatment far outweigh the disadvantages. The only downside to the treatment is the inconvenience of having to plan our schedule around the treatment day and manage the logistics of deliveries and arrangements.	Patient/ Family	Logistics
Time consuming, can't go anywhere whilst it's being done.	Patient/ Family	Time consuming
It's such a long infusion, it's a whole day gone and usually feel very tired afterwards	Patient/ Family	Time consuming Tiredness
Only when Healthcare at Home mess up the deliveries.	Patient/ Family	Deliveries
Only disadvantage is when Healthcare at Home mess up the medicine stores delivery and there is lack of communication with me as a parent who administers the drug independently at home.	Patient/ Family	Deliveries
After about a year my veins became unsuitable for accessing. There was a huge stress associated with treatment at the time as I had to return to having treatments in hospital so an anaesthetist could try to access them. In the end I came off the MAA for a few months while I waited for a port-a-cath insertion. Since then there have been no problems. The port-a-cath is quick and unobtrusive (whereas a cannula restricts arm movement) which means I can do my usual activities while been treated.	Patient	Veins
The advantages of treatment far outweigh the disadvantages, which if any, is the length of time to infuse.	Patient	Time consuming
Just my veins but off the top of my head that it is all that I can think of.	Patient	Veins
When I first started treatment, I had to deal with the reality of missing some university classes as I was in the hospital for a full day per week. This took some adjustment, my university had to provide digital versions of the lectures to make sure I wasn't missing out on lessons, but it was manageable. Similarly, when I started working, I had to figure out a way to work remotely for one day per week. Fortunately, remote working is common in the software developer domain, so this wasn't much of a problem.	Patient	Time consuming Missing classes Work on infusion day
This is mostly organisational. Obviously taking time to get cannulated each week is a bit of a nuisance, but glad I can have it at work (and I wouldn't do it if I didn't feel it was good). I do worry about flexibility around having the treatment in the future, as I work in an industry where I might move around a bit, or be on shoots one week etc. And it's been a bit of an issue as I'm not always home with my drug and getting the nurses to come with the drug has been troublesome at times (e.g. when I went home to my parents for a week for Christmas).	Patient	Logistics
It takes a day out of my week. But I think this is a small price to pay to live a better and healthier life. I have had a few reactions to the treatment, but these are easily managed and I do take a pre-med to help prevent this. Occasionally, I am unable to have my treatment on the day I would like it due to the availability of nurses.	Patient	Availability of home-care nurses Minor reactions Takes a whole day
The only problems I have had with treatment are well documented and relate to the level of service provided by the home care nursing company- the medication in itself is perfect.	Patient	Availability of home-care nurses

Disadvantages or problems for the child with treatment	Patient/ Family	Disadvantages
The treatment takes up the majority of my Fridays, where I must rest as a result of the medication I receive beforehand.	Patient	Takes a whole day
Pains in hands.	Patient	Pain
No disadvantages.	Patient	None
- The only disadvantage I have found with treatment is the way it is administered, via an IV drip. My veins are difficult to cannulate which makes each infusion a challenge and spending a day each week on treatment makes it harder to plan things like holidays. I used to get very tired on infusion days, but I am able to tolerate them better now. These disadvantages are minor compared to the benefits of treatment I have experienced, and my weekly infusions are now routine and a regular part of my life.	Patient	Holidays Tiredness Veins
I have not had any negative effects from having the treatment. Sometimes, just after treatment I may have some stomach issues, but I do not classify them as negative as it clears up quickly.	Patient	Stomach issues
Slight nausea sometimes during treatment and lack of mobility as line usually inserted in right arm which prevents me using crutches.	Patient	Lack of mobility during infusion Nausea

THOUGHTS ABOUT THE MANAGED ACCESS AGREEEMENT

We asked: If you have been part of the English Managed Access Agreement, please give your thoughts and comments on this programme

- Consensus in all responses about the MAA was that parents/patients would do anything to keep receiving treatment with elosulfase alfa
- Patients/parents were aware the MAA is the only way of getting treatment with elosulfase alfa and were worried about its future availability
- There were concerns about the way the clinical measures decide if the patient continues treatment, and believed criteria looking for constant improvements does not reflect this degenerative disorder

Thoughts about the Managed Access Agreement	**Key points**
My child has been part of this programme for over 2 years, it has helped him a lot and I think they should continue this; it is necessary.	Should continue
This was the only way to get Vimizim without directly purchasing it I understand.	Only way to get treatment
We hope the treatment will be funded by NHS England post trial.	Should continue
The MAA has been interesting. Whilst on one hand it has granted access to this vital drug, and for that we are forever grateful, it does have some shortcomings. Psychologically the message that if you can't walk as far means the treatment isn't working is somewhat over-simplified and worrying for all involved. This is a pressure that a child, or anyone for that matter should not have to endure. The threat of treatment being taken away is damaging for all involved. Life is like a roller coaster. Morquio brings enough challenges for all of us without this as well. I worry about the long-term psychological impacts this will have on our brave children who have to put up with so much. Vimizim is not a pill. It is spending four hours a week hooked up to a drip. For many it is dealing with allergic reactions, tolerating needles, impinging on leisure time. It is stressful. Genuinely parents would not put their children through this if they did not see the benefits. Morquio is a complex, multi-faceted condition. Patients and parents know the most about the benefits treatment has and the impacts it has too. Listen to them and you'll learn more than set of statistics recorded twice a year. I accept the need to gather more evidence, but the evidence is compelling and overwhelming. Our children have experienced a better life, less pain, more independence. More freedom, a better quality of life by far, and vitally a significantly more hopeful future. You can't put a price on that. Lastly Morquio is a progressive condition which worsens as patients get older. The MAA does not take account of this. Measures feasibly could worsen over a decade, and still be far better than they would have been without treatment. This aspect of the MAA is unfair and discriminatory. Taken to its logical extreme its like expecting a 60-year-old to walk as fast as they did when they were 17. And that's without them having a degenerative disease.	Hopeful future No parent would put their child through it if they would not see benefits – do not rely only on statistics Only way to get treatment Oversimplified Tests need to take into account this is a degenerative condition Threat of treatment taken away Worry about psychological health
For the most part I think the MAA has worked well for us, but I don't think the baseline tests are "fair". This is a degenerative condition. Comparing my child's current results with when they were a five-year-old seems like setting them up to fail. All children change a lot between five and fifteen.	MAA has worked well Tests need to take into account this is a degenerative condition

Thoughts about the Managed Access Agreement	Key points
We are grateful that a way was found to provide treatment via the Managed Access Agreement when it became clear that the approach used for assessing new treatments proved to be unsuitable for assessing treatments for ultra-rare conditions such as MPS IVA. However, we are frustrated that we are now again facing uncertainty regarding the future for our child as the prospect of treatment ending again becomes a possibility. In a year when we are making decisions for our child regarding surgical interventions based on his current state of health it is frightening to think that the treatment could end within months and the surgery may prove worthless as his overall health declines. At the start of the managed access agreement we were given to understand that it would run for 5 years and then the new data collected during this time would be evaluated as part of the assessment for treatment longer term. However, we now find that the results of only 3.5 years are being analysed for the current review of Vimizim and we are facing a cliff edge with the outcome very uncertain. My child has participated fully in the regular assessments required as part of the MAA and these have on the whole not been too onerous and have generally been carried out as part of his routine health monitoring anyway. However, when the data from these assessments is being reviewed it must be remembered that MPS IVA is a condition where the effects can readily fluctuate from day to day and the way that individuals with the condition are affected varies considerably from one person to another. We accept that the MAA was a necessary tool to progress the implementation of granting access to Vimizim following the successful clinical trial but still have concerns that the particular factors at play in ultra-rare diseases are not being adequately taken into account in the evaluation process. These being 1) the cost per patient is disproportionately high compared to mainstream treatments as there are far fewer patients against whom the high costs of development will be recouped; 2) the extremely small patient group worldwide let alone in England makes it very difficult to get the quantity of data usually used for modelling and analysis; 3) the effects and symptoms of MPS IVA and the response to treatment has a high degree of heterogeneity among patients, which contributes to the difficulty in analysing the data; 4) MPS IVA is a degenerative condition so the treatment would be considered beneficial by patients and their families if the degeneration is slowed or halted, rather than always looking for an improvement. The fact that this last point was not taken into account in designing the criteria in the MAA is a significant flaw in the process, where the criteria are heavily based around seeing an improvement.	Flaw in the process: a benefit is to halt/slow down degeneration, but criteria is looking for an improvement Frightening that treatment may stop Should continue Tests need to take into account this is a degenerative condition
The English Managed Access Agreement programme has been fine. The only criticism would be to allow a certain number of weeks off a year, to allow for holidays.	Holidays
I have found the MAA to be a incredibly stressful experience, BUT I will do whatever is needed, anything NICE need me to do in order to keep receiving the drug that was quite literally changed my life, and is giving me a quality of life that I never dreamed possible. I do not want to go back to a life dependent on wheelchairs, stair lifts, and somebody wiping my bum when I've been to the toilet.	MAA stressful but patient would do anything to keep receiving the treatment that has changed his life
It is very hard to be tied to the MAA BUT we are happy to take on any protocols needed to guarantee that out daughter continues to receive treatment - our lives have been transformed by this drug and it is allowing our child to live a full and completely independent life. Something that 4 years ago when we were reliant on wheelchairs and stairlifts etc we never would have thought possible. The biggest drawback is the fact that our specialist centre is a 5- hour drive away so we have to take time of work equaling 2 days as parents and education as a patient per compulsory hospital appointment.	Difficult but happy to do it to keep daughter on treatment that has transformed her life

Thoughts about the Managed Access Agreement	Key points
I am incredibly grateful to be given access to the milestones and achievements I have been able to receive through the access to Vimizim through the MAA. However the strict regulations with regards to the allowed number of missed treatments can leave patients with a fear of treatment being withdrawn, for things like taking a holiday, not wanting to take time off when starting a new job, or things out of our control, such as lack of nursing staff, even if Vimizim is showing an improvement. There is also the case where individuals who started Vimizim later in life have seen some progression in their condition before starting Vimizim and some symptoms such as arthritis will progress if it started before treatment, despite taking Vimizim, which could be at the patients disadvantage with measures like the 6MWT, even if they feel an improvement in other areas of the condition such as endurance.	Fear of treatment withdrawn if not meeting criteria Holidays/ time off work Older patients at a disadvantage with measurements
Travelling to the hospital for appointments 3–4 times a year is a bit of an inconvenience to me. It can mean that I need to take extra time off work. There is always a bit of uncertainty that if I don't manage to meet the criteria, the treatment won't be available to me anymore. I have to plan things more carefully as I can only miss so many infusions in a year.	Fear of treatment withdrawn if not meeting criteria Travelling to appointments Planning
It's been ok - bit annoying having to do the tests (especially having to bring in my walker for the walking test, as that means having a person come with me), so hoping that will end - but again, wouldn't be doing it if I didn't think it was all worth it, so it's alright I guess.	Tests annoying but it is worth it
- I am lucky to have been part of the Managed Access Agreement and I understand the need for it to gather more long-term evidence on the benefits of Vimizim across a wider range of patients. I am proud of being able to contribute to the essential research of such an ultra-rare condition. - I found it interesting to see how the benefits I was experiencing were also reflected in the clinical test results**.** - Having said that, I felt that the endurance tests (the 6 minute walking test and the lung function test) didn't necessarily offer a true reflection of the reality of the benefits as the results depended on how I was feeling at that particular moment in time. Repeating the same test, a day earlier or a day later could produce different results. I find that anecdotal evidence of changes to my day to day life were certainly representative of the benefits of treatment and how it has improved my quality of life significantly on a daily basis.	Benefits reflected on clinical tests Tests need to take into account this is a degenerative condition
I have been part of the English Managed Access Agreement since May 2016. For me it has been a tremendous programme that has supported me from day one. It is well structured and allows me to participate with the treatment by monitoring my health changes and allowing me to see these changes as they are recorded. Attending assessments and completing questionnaires regularly can help monitor the benefits and also allow me, as a recipient of Vimizim, to see how it is actually benefiting me and allows me to discuss issues with my Consultant or with the MPS Society. I fully appreciate that there are restrictions on how many treatment days can be missed within the programme but to be fair, if you are going to take medication that improves your health, life, self-esteem, why would you wish to miss any?	It has supported him from day one
From what I know the agreement seems to work. Missed infusions is a worry, particularly when we used to go on holiday for four weeks, and if I have had a treatment-preventing illness. This being said, we have never had any major problems and if anything, the worry of been taken off the MAA is testament to its significance to me.	Fear of treatment withdrawn if not meeting criteria Holidays

BREAK IN TREATMENT

We asked: If you have ever had a break in treatment for more than three weeks, please tell us if you noticed any effects of being off treatment, what were they? Please include how long you were off treatment for and how soon you noticed any effects.

- Patients health deteriorated as soon as they took a break in treatment, even when the break was as short as one week, or when missing one infusion
- Patients felt fatigued, their stamina decreased, breathing problems and pain returned, and vision deteriorated. Mobility decreased, with at least two patients having to go back to using a wheelchair

Effects of being off treatment	Duration	Impact
1-week break and you can notice him slowing down and getting tired quick and having more pains his postures different and his speech also.	1 week	Pain Fatigue Speech
We had a six-week break. He developed cornea clouding during this time for the first time ever. His movement noticeably stiffened and became more laboured. This reverted when he restarted treatment and the corneal clouding has remained stable to this day, 5 years on.	6 weeks	Mobility Vision
Yes, during the break between the trial and the MAA beginning. We saw an increase in tiredness, and stamina. Reduced ability to do things like climb stairs, and a large increase in breathlessness and noisy breathing while doing any sort of sustained activity such as walking.	Between trial-MAA	Breathlessness Fatigue Mobility Stamina
My child had to stop treatment with Vimizim for a period of seven weeks due to the suspension of the compassionate use programme during delays in the original evaluation process. This meant we were unfortunately in a position to observe the effect of the withdrawal of treatment on my child. After about 4 or 5 weeks without treatment we did begin to notice a reduction in stamina and mobility. By the time the treatment resumed after a break of seven weeks, my child experienced a reduction in stamina, clearly "running out of steam" much sooner than we had been used to. Around four or five weeks after the resumption of treatment, we noticed that he was improving again, although not yet back to the same fitness level he enjoyed previously.	7 weeks	Mobility Pain Stamina
I've been off treatment for a few weeks before but didn't notice any immediate effect.	A few weeks	None
There was a short break in treatment, when funding was in question. My daughter did start to feel lethargic when not on treatment.	Short break	Lethargy
I had a break of 6 months when there was a problem with my port after about 3 weeks, I had decreased stamina increased pain no energy decreased vision and had to go back to a fulltime wheelchair. I was quite suicidal.	6 months	Energy Mental health Mobility Pain Stamina Vision Wheelchair

We had to stop treatment for approx. 6 months about 18 months ago as there was a problem with the port-a-cath that was inserted. Within 4 weeks our daughter was back to needing full time wheelchair use and stairlifts, profiling bed and her vision had deteriorated to the extent that she needed extra time building into her exams and a scribe as she was unable to see adequately enough. She was also back to chronic long-term pain in all joints. Her energy levels fell through the floor and she needed to leave school early every day to come home and sleep. Her stamina was non-existent.	6 months	Energy Fatigue Mobility Pain Stamina Vision Wheelchair
Yes, I noted the effects wear off around the seconds week. I reverted to not been able to walk and struggling to exert myself.	2 weeks	Mobility
The only break I had was between phase 4 of the trial and the start of the compassionate use programme. I think this was around 6 months. Six months after my final visit to receive the enzyme replacement therapy drug, I had noticed significant decline in my independence in performing everyday task. I noticed that once again, visits to the local supermarkets left me fatigued for the rest of the day. I again planned my day and my activities according to what my body allows me to do with minimal discomfort. Milestones I had reached whilst on the enzyme replacement therapy trial, after a short break, became challenges. I found myself held back from reaching them.	6 months	Fatigue Independence
I was off the treatment for 9 weeks after the trial had ended and before the Managed Access Agreement was formed. I didn't notice any changes straight away, but I feel like my sleep went back to how it was before the trial started... I was sleeping more, but not necessarily feeling refreshed when I woke up, indicating a poor quality of sleep.	9 weeks	Sleep
Energy recovery is slower whenever I miss a treatment. More noticeable if I have to miss multiple treatments.	6 months	Energy Mental health Pain Stamina, mobility Vision Wheelchair
Two weeks was the maximum. I could feel my energy slipping back.	2 weeks	Energy
I have never had a break in treatment for more than three weeks. However, I did notice a difference in energy levels and pain after missing a single infusion.	1 infusion	Energy Pain
I had a forced break (medical reason) from Vimizim and had to skip two infusions consecutively due to a viral infection. I noticed by the second week, that I was generally more achy than usual, that my arthritis took longer to clear up than usual and generally felt run down. I also noticed that I was more tired and restless in bed. This improved as soon as I was able to restart Vimizim and my general health returned to how it was prior to the break.	2 infusions	Fatigue Pain
I went off treatment for several months. Within two weeks we (my family and I) noticed a significant decline in activity, concentration and interest in leisure activities. My academic results dropped over this period and I felt the worst (in terms of general lack of interest and self-perception) I ever have.	Months	Activity Concentration Learning

STOPPING TREATMENT

We asked: *Why did you/your child stop treatment?*

	Age treatment started (years)	Time on treatment	Reasons
Patient 1	1–5	8 years 1 month	Port-a-cath had been removed due to infection, child did not want another one. Impact of long infusion on child. Felt it was right to stop the infusions and let child attend school full time and feel as normal as their friends.
Patient 2	11–15	1 year	Anaphylactic reaction.
Patient 3	31–40	12 months	Did not feel the benefit they wished for.

HEALTH CHANGES AFTER STOPPING TREATMENT

We asked: How has your/your child's health changed since coming off treatment? Please tell us how long it has been since your/your child's last Vimizim infusion.

	Last infusion	Has my/my child's health deteriorated?
Patient 1	June 2017	Yes, my son has deteriorated physically and is not very mobile.
Patient 2	5 years ago	Not as strong as I was when I was on the trial. It gave me a better quality of life and now I feel that has worsened after I stopped.
Patient 3	2013	Remained same.

EDUCATION/EMPLOYMENT OF PATIENTS WITH MPS IVA

We asked about individuals educational and employment status using a multiple choice question.

(Answers from patients who chose 'Other' have been categorised and presented below. Categories that applied to no patients are not shown).

The majority of patients (83%) were in education, employed or retired following a long career (Figure 3,4). Only two patients were unable to work due to their health.

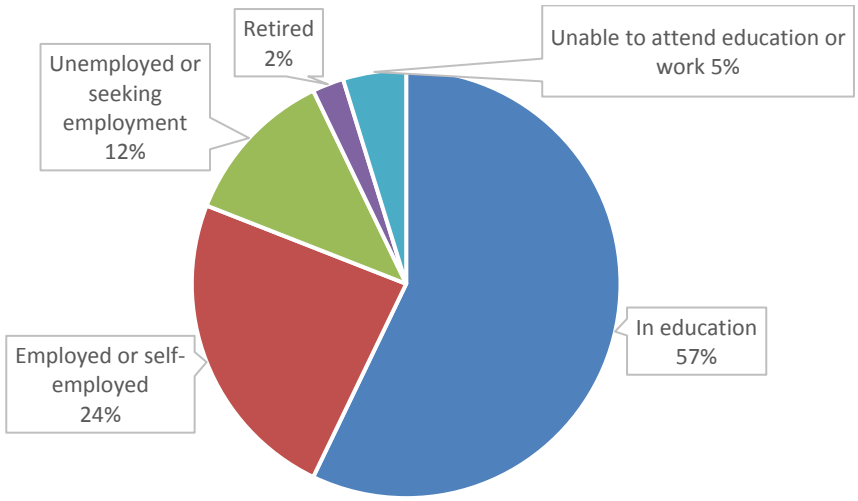


FIGURE 3. PATIENTS' OVERALL EDUCATION OR EMPLOYEMENT STATUS

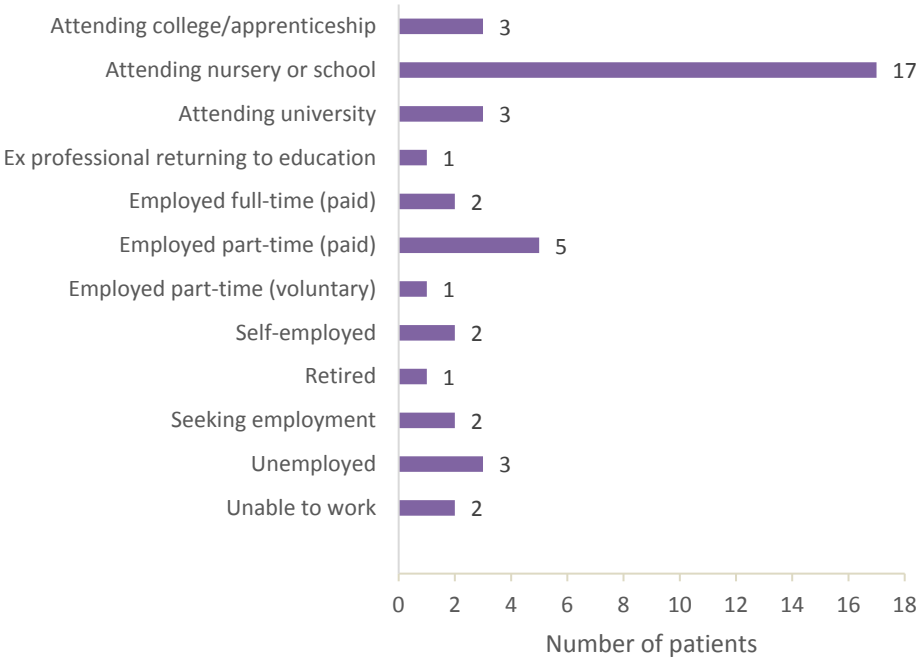


FIGURE 4. PATIENTS' EDUCATION OR EMPLOYEMENT STATUS BY CATEGORY

Why is the patient not able to work?	
Patient 1	I finished education when I was 18. I'm not or have I ever been capable to work due to my disability.
Patient 2	Was unable to find a volunteer post and unable to work due to health problems.

FURTHER COMMENTS

We asked: *Do you have any further comments on Vimizim treatment?*

Comments on Vimizim treatment

The treatment has helped my child a lot, and I think it will keep helping him in a longer term.

I never miss my treatment as it keeps me going, **can't live without it as is so good.**

I wish everyone who is offered the treatment would accept and **see the results for themselves** before deciding not to have the treatment.

Life changing in every possible way and magical for my child.

Being on Vimizim has given my son the **best possible start in life** and has **delayed any negative effects** that his condition can bring upon him.

He has **improved significantly** in his walking and lung function tests. He would need to pause continuously before, where now he just carries on walking.

We need this treatment to continue to give our child the best chance of a longer life.

Vimizim **gives hope where there is none**. Hope is all we had. The drug **works brilliantly for my daughter**, but unfortunately, I felt my son couldn't cope with the demands it took from him.

I hope it continues to be made available.

Given the degenerative effects of MPS IVA **I firmly believe that my child would be in significantly poorer health**, with even less stamina and mobility **if he had not been on treatment**. **He would have no prospect of surgical interventions** for those aspects of the condition which are currently troubling him and **his quality of life would be significantly lower**.

Vimizim has given my daughter the prospect of a near normal life. I never imagined she would go to **University** and be so **independent**. She drives her own car, enjoys a good social life, and is determined to be happy and as mobile as possible. **Vimizim has played a crucial role in her life.**

Please allow us to keep accessing the drug that has changed our lives and given us a life.

Comments on Vimizim treatment

Vimizim **has transformed our daughters and consequently our lives**. To have a child who is permanently reliant on a wheelchair and stairlift , who could not attend a full day in school and had extremely poor vision **suddenly become totally independent and walking EVERYWHERE, abandoning her wheelchair and stairlift, going out with friends, driving a car and holding down a job alongside college and be pain free is truly amazing**.

I have gone into detail statistically, about the ways in which Vimizim has had an impact on my life. However, **the benefits I have seen from Vimizim, cannot be restricted to quantitative data**. **I have reached milestones in my mobility, and have managed to build a life for myself by gaining an education and building a career**, and it is doubtful whether **this would have been possible without the strength, confidence and hope for the future that Vimizim has given me**.

This shows that **Vimizim is compatible with everyday life**, and **a sufferer of Morquio's syndrome, is fully capable of building a life and living the way ordinary people do, with the right treatment**.

I can't say I'm ready to run marathons yet, but I am able to live my life, like any other 27 year old is able to, and I can only hope that this isn't taken away from me, over something which isn't in my power to control. Everyone should be given a chance to achieve their potential, and for suffers of Morquio's syndrome, Vimizim is a step towards this.

I was taking the enzyme replacement therapy drug regularly for just over two years, and **it was the best thing that has ever happened to me**. I could accomplish the ordinary and for me, that was extraordinary. Increased physical independence and mobility is a pipe dream for Morquio's Sufferers. But I lived that dream and **I hope that many others are given the opportunity to do so.**

This is quite a time-consuming treatment. **I wouldn't continue with it if I didn't think it was helping me.**

Just **that I'm a bit scared of losing it, as I've finally gotten into the industry I want to be in, and I'm working well doing stuff I love, and I worry that if I lose Vimizim** my energy levels will go down again, and that I perhaps **won't be able to keep up in work further**.

I am **thankful and grateful that this treatment is available**. And I **hope it continues** to develop more and helps others like me.

My whole life you go everywhere to appointments it is all bad news and doom and gloom, but **when Vimizim came about it was a ray of hope, to see yourself improve when all you know is bad news it has been amazing and I worry less about the future**. Also, no operations which would of happened if not for Vimizim so saves the health service money in the long run.

It feels like I have been given a second chance. **I see life now as an opportunity to find meaning and enjoyment**, where before I was in dread and constant pain. I now feel like, with my medication **I can achieve the things I came to realise I would miss out on** as my health started to deteriorate before I began to receive Vimizim.

Over the course of my adult life, even with as much positivity as I could muster, there were certain setbacks I have encountered that could have been avoided had I been well enough to do so. I now feel optimistic that the goals of which I have had no choice but to compromise on now seem completely manageable with no pain and increased mobility.

The only other thing I have to say is thank you. I have my life back!

Comments on Vimizim treatment

No benefit for me. Maybe more beneficial for someone younger.

It has made me a new man and I am scared that I will go backwards if stopped.

- It is no exaggeration to say that **the effects of Vimizim has been life changing**. It has given me a **new lease of life that I have never experienced before and did not expect to experience**.
- It's not easy giving up a day every week for treatment, but **the benefits by far outweigh the challenges** of weekly infusions. I wouldn't have persisted if it hadn't made such a huge difference to my wellbeing and quality of life.

- The benefits are not only physical. **I have a more positive outlook on life** as I'm enjoying life more and have more confidence in myself and what I am capable of doing.

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

Throughout my life I never received any particular treatment related to Morquio or information about the condition. It was only when a locum GP agreed to refer me to see a specialist in this disease, that I became aware of the newly trialled ERT Vimizim. I did not know what to expect when I was given a chance to try this new treatment, as I felt maybe I was too old and as it a progressive disease maybe it was too late for me to notice any difference.
Yet **within 4 months I started to notice what to me was a huge improvement**: the strengthening of my arms and wrist and the power it gave me to **do things that before I relied on others** e.g. pull myself upstairs without someone helping me. I also **slept better** meaning that I wake up alert and not struggling out of bed. **I participate at home more with chores,** etc. and that makes me feel useful**. I have not had a cold or flu in such a long time**, which previously were debilitating and took a long time to recuperate.

My mobility has improved - I know that I will never run marathons but to be able to walk more without the need to rest has been such a boost. **Vimizim, even at my age has improved my life beyond any expectations** I could ever have imagined and not just **physically but also mentally** as my self-esteem has also had a boost.

I have written an additional letter that best outlines my entire Vimizim experience, that I have submitted to the relevant people.

REFERENCES

1. National Institute for Health and Care Excellence. Managed Access Agreement. Elosulfase alfa for treating mucopolysaccharidosis type Iva. November 2015. Available at: https://www.nice.org.uk/guidance/hst2/resources/managed-access-agreement-december-2015-2238935869 (Accessed on 4th March 2020).

MPS IVA patient and caregiver experience of treatment – UK survey

Rare Disease Research Partners (formerly known as MPS Commercial) are working with the MPS Society UK to collect information to support the National Institute of Health Care Excellence's (NICE) review of Vimizim treatment in England.

Purpose of the survey

The survey includes questions about your experience of Vimizim treatment and will be used as part of the evidence that Rare Disease Research Partners and the MPS Society will submit to NICE to support the continued access to treatment in England.

Who can take part?
The survey is open to those aged 16 years and over resident in the UK that:

- have MPS IVA and are currently receiving Vimizim treatment
- have MPS IVA and have received Vimizim treatment in the past (including taking part in a clinical trial)
- care for/are the parent of an individual with MPS IVA who is currently receiving Vimizim treatment
- care for/are the parent of an individual with MPS IVA who has received Vimizim treatment in the past (including taking part in a clinical trial)

We welcome responses from parents or caregivers, even if your child (aged 16 years or older) has also responded to the survey, as representation of the views of both patients and parents/caregivers will be extremely valuable in presenting a broad view of the effects of treatment to NICE.

Confidentiality
Rare Disease Research Partners will protect the confidentiality of information gathered during this survey in accordance with applicable data protection legislation. Your identity (your name) will not be collected in this survey.

The de-identified and aggregated data from this survey will be shared with NICE. NICE may use this information in their review of Vimizim treatment being conducted in 2020 and share it with the parties involved in the review. NICE may publish this data. It is NICE's usual practice to make the evidence submitted for a review of a highly specialised technology, such as Vimizim, publically available. Your or your child's identity will not be shared with NICE and the answers you provide will not be identifiable to a specific person.

You can view our data protection policies here:
https://rd-rp.com/wp-content/uploads/2019/12/GDPR-Data-Protection-Policy.pdf
https://www.mpssociety.org.uk/policies

Voluntary participation and withdrawal

Your participation in this survey is voluntary. If you do decide to take part, please indicate your consent below. You are free to withdraw from the survey at any time without giving a reason.

Further information

If you have any questions about the survey please contact us on info@rd-rp.com
Rare Disease Research Partners, MPS House, Repton Place, White Lion Road, Amersham, HP7 9LP

Your consent

Q1 Please indicate that you have read and understood the information above and are happy to take part in the survey by indicating your choice below

O I consent to take part in the survey

O I do not consent to take part in the survey

Q2 Are you:

O A person with MPS IVA?

O The parent or carer of a person with MPS IVA?

Q3 Where do you live?

O England

O Wales

O Scotland

O Northern Ireland

Q4 How old is the person with MPS IVA (in years)?

_____

Q5 How old was the person with MPS IVA when they started treatment (in years)?

_____

Q6 Please choose the option that best describes you / your child

O I am / my child is currently receiving treatment with Vimizim (**please go to Question 10**)

O My / my child's Vimizim treatment has been temporarily stopped due to medical or other issues (**please go to Question 9**)

O I have / my child has received Vimizim treatment in the past, but am no longer on this treatment (**please go to Question 7**)

Q7 Why did you / your child stop treatment?

Q8 How has your / your child's health changed since coming off treatment?

Q9 Please tell us how long it has been since your / your child's last Vimizim infusion

Q10 For how long in total have you / has your child received Vimizim treatment?
Please include all treatment received (e.g. as part of a clinical trial, managed access agreement or compassionate use programme). Include any past treatment if you are no longer receiving Vimizim.

_____

Q11 Thinking back to when you first started Vimizim treatment, what effects of treatment did you first notice and how soon after starting treatment did you notice these effects?
This can include any positive or negative effects you / your child experienced

Q12 Have these effects of treatment continued, improved over time or are they no longer seen?

Q13 What have been the main benefits of treatment to you / your child?
Please be as specific as possible and give examples of the benefits you have noticed.

Q14 If you /your child have been on treatment or had received treatment for more than two years, what are the sustained benefits of treatment?

Q15 Has being on treatment had any impact on your /your child's education?
For example, have the number of hours or days attending education changed? Has the level of support in education changed? Has there been a change in ability to participate in extra-curricular activites? Please give specific examples.

Q16 Has being on treatment had any impact on your /your child's employment?
For example, has your / their ability to work changed? Have the number of hours or days attending work changed? Has the level of support in work changed? Please give specific examples.

Q17 Has being on treatment had any impact on your /your child's leisure time?
Please give specific examples of any impacts on your or your child's time outside of school or work and at weekends.

Q18 Has being on treatment had any impact on your /your child's independence?
Please give specific examples.

Q19 **Do you have any independent evidence of the changes you have talked about that you could share with the MPS Society?**
Examples would be things like:

School reports Blogs, social media posts, youtube videos where you have talked about the effects of treatment or coming off treatment
Please contact Sophie Thomas at s.thomas@mpssociety.org.uk or

Alex Morrison at a.morrison@rd-rp.com to discuss any materials that you think you may be able to share.

Q20 Please tell us about any disadvantages or problems you have had with treatment

Q21 If you have been part of the English Managed Access Agreement, please give your thoughts and comments on this programme

Q22 If you have ever had a break in treatment for more than three weeks, please tell us if you noticed any effects of being off treatment, what were they?

Please include how long you were off treatment for and how soon you noticed any effects.

Q23 Are you / is your child:

- O Too young to attend school
- O Attending nursery or school
- O Attending college/apprenticeship
- O Attending university
- O Seeking employment
- O Employed part-time (voluntary)
- O Employed part-time (paid)
- O Employed full-time (voluntary)
- O Employed full-time (paid)
- O Unable to attend education / work (please give details)
- O Other (please give details)

Q24 Do you have any further comments on Vimizim treatment?

Please return to Alex Morrison

a.morrison@rd-rp.com

Rare Disease Research Partners, MPS House, Repton Place, White Lion Road, Amersham, HP7 9LP

The educational journey of individuals with MPS IVA Morquio Disease

Sophie Thomas,[1] Alex Morrison.[1]

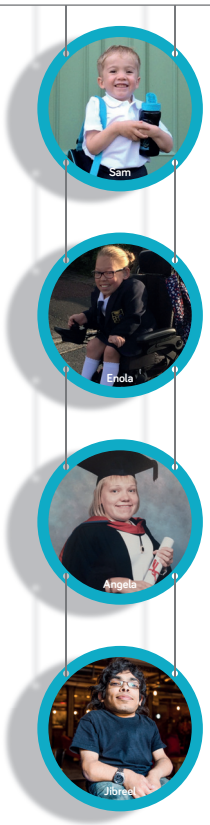
[1]The Society for Mucopolysaccharide Diseases (MPS Society), Buckinghamshire, UK

Introduction

- Morquio syndrome (MPS IVA) is an extremely rare lysosomal storage disorder which is caused by deficiency in the enzyme *N*-acetylgalactosamine-6-sulfatase.[1]
- Individuals with Morquio experience progressive skeletal and non-skeletal manifestations (including respiratory disease and cardiac disease), which can impact upon their functional capacity, mobility and quality of life.[2]
- The aim of this project was to determine the educational and employment history of individuals with Morquio.

Methods

- Ninety-nine individuals with Morquio, identified by the MPS Society, were invited to take part in the survey via postal questionnaire in April and May 2014.
- A specifically designed questionnaire was used to assess the individual's educational attainment and need for support from primary through to further education as well as their employment history.



Primary school (n=46)

Secondary school (n=30)

Further/higher education (n=21)

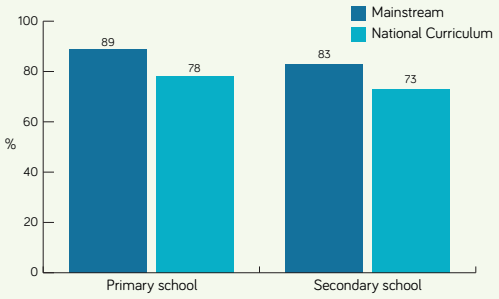
Employment (n=16)

Figure 1. The number of responses received for the educational and employment journey of individuals with Morquio.

Results

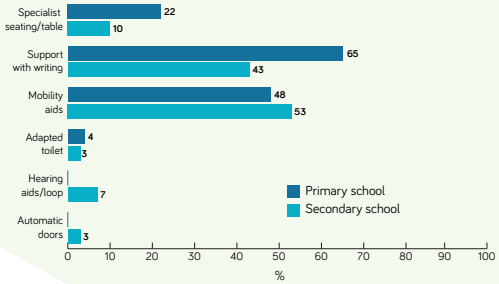
- Forty-six individuals completed the questionnaire (46%).
- There was an equal number of male and female respondents, aged 4 years to 56 years (mean 21.8 years).
- The number of responses received varied at each educational stage (Figure 1); data were calculated using these values unless otherwise specified.
- The majority of individuals with Morquio attended mainstream schools and followed the National Curriculum (Figure 2).

Figure 2. Most individuals with Morquio attended mainstream school and followed the National Curriculum



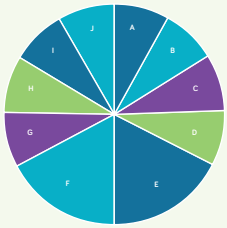
- Sixty-one percent of individuals were issued with a statement of educational need (SEN) in primary school; the mean age at issue was 5.3 years (range 3–12 years).
- By secondary school 66% of individuals had a SEN; the majority of which had been issued in primary school.
- Seventy percent of individuals needed additional help at primary school compared to 63% at secondary school.
- The most common requirements at primary school were help moving around the school (37%), getting ready for physical education (PE) (35%) and with writing (26%).
- Similar needs were reported at secondary school: moving around school/carrying things (43%), personal care/dressing (40%), writing (27%), PE (20%) and one to one support (17%).
- A range of specialist equipment was used in primary and secondary schools, alike (Figure 3).

Figure 3. The range of specialised equipment used in primary and secondary school



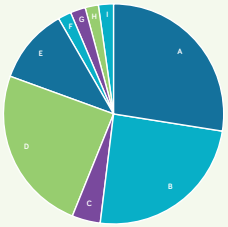
- Support with writing in primary schools included the use of typewriters/laptops/word processors (35%) and pencil grips (20%); typewriters/laptops were commonly used in secondary schools as well (30%), although the use of pencil grips had fallen (7%).
- In primary school 13% of individuals used wheelchairs, 20% used rise and fall chairs, 7% used scooters/buggies and 4% had walking frames.
- Wheelchair use (including rise and fall wheelchairs) was 40% in secondary school and 10% used scooters.
- There was considerably less input from professionals in primary school with no reports of occupational therapist, physiotherapist, special educational needs co-ordinator (SENCO) or educational psychologist involvement.
- In primary schools the most frequently seen professionals were advisory teachers (hearing and physical disabilities) (Figure 4).
- The most frequently seen professionals in secondary school were: occupational therapist, physiotherapist, SENCO and educational psychologist (Figure 5).

Figure 4. Professional involvement in the primary school setting



- A Hydrotherapy teacher (8%)
- B Social worker (8%)
- C MPS Society advocacy worker (8%)
- D Transitions officer and counselling (8%)
- E Hearing advisory teacher (17%)
- F Physical disabilities advisory teacher (17%)
- G Special school outreach support worker (8%)
- H School paediatrician (8%)
- I One-to-one support worker (8%)
- J Outreach nurse (8%)

Figure 5. Professional involvement in the secondary school setting



- A Occupational therapist (27%)
- B Physiotherapist (24%)
- C Speech and language therapist (4%)
- D SENCO (24%)
- E Educational psychologist (11%)
- F Hearing advisory teacher (2%)
- G Physical disabilities advisory teacher (2%)
- H Family support worker (2%)
- I Other (2%)

- Fifty-four percent of individuals felt that the number of medical appointments impacted on their primary education, versus 46% (13/28) on secondary education.
- Overall 91% reported their experience of primary school as positive, compared to 86% (24/28) positive for secondary school.
- Eighty-five percent (23/27) of individuals were studying for, or had gained, GCSE qualifications. A further 11% had gained other secondary school qualifications and only 1 individual had not taken exams at school.
- Twenty-one individuals were in or had completed further education, of which 47% were studying for or had gained honours or higher degrees (Masters and PhD).
- Only one individual had gone straight from secondary school to employment.
- Of the 16 individuals who had completed their education, 81% were currently employed or had previously been employed.
- Of those currently employed, or who had previously been employed the roles were varied (Figure 6).
- On the whole, individuals felt that they were well supported by their employers (Figure 7); workplace adaptations were in place and time off for medical appointments/infusions was permitted.

Figure 6. Employment history of individuals with Morquio

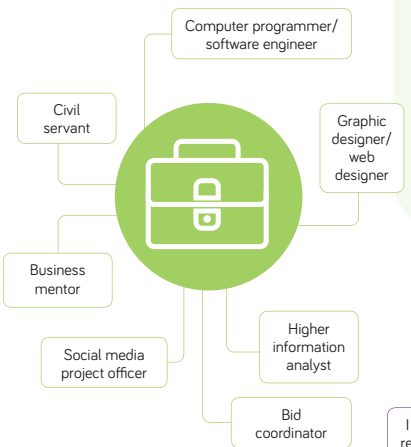


Figure 7. Experience of the workplace in individuals with Morquio

Conclusions

- The educational needs for most individuals with MPS IVA were met by mainstream schools.
- Individuals received very little specialist input in primary school, but were well supported in secondary school.
- Although half of the individuals surveyed felt that medical appointments impacted on their education, most had gone onto further education and a high proportion attended university and entered employment.
- Most individuals had a positive experience in the workplace.

References

1. Hendriksz C, et al. 2015. Am J Med Genet A;167A(1):11.
2.Hendriksz C, et al. 2014. Orphanet J Rare Dis;9:32.

Acknowledgements

- Medical writing and editorial support was provided by Jacqueline Adam, PhD, MPS Commercial.
- Debbie Cavell, MPS IVA Advocacy Officer at the MPS Society, for all of her support and work with individuals and their families.

Society for Mucopolysaccharide Diseases
www.mpssociety.org.uk

Appendix D - professional organisation statement template

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Highly Specialised Technology Evaluation

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Birmingham Women's and Children's NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ☑
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ☑
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No links to declare

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What is the expected place of the technology in current practice?

Mucopolysaccharidosis Type IVa (MPS IVa) is a very rare lysosomal storage disorder and therefore currently managed only by the designated LSD centres. As a paediatrician I am qualified mostly to comment on the treatment of children with MPS IVa and I will restrict my submission to my experience with treating children with MPS IVa but it is essential that NICE appreciates adults with MPS IVa make up approximately 50% of the treated population and may include a discrete group of patients with attenuated disease who may benefit to a different degree and in different ways than children. To the knowledge of the paediatric LSD centres there are no additional diagnosed children in England for whom elosulfase alfa has not been offered and therefore we would not anticipate a surge in demand for this treatment upon the release of a positive recommendation.

Children with MPS IVa are currently treated at one of the three paediatric designated highly specialised service centres: Great Ormond Street Hospital in London, Royal Manchester Children's Hospital or the Birmingham Children's Hospital. Patients are treated according to agreed guidelines that are very much based around the elosulfase alfa managed access agreement and there is little variation in practice across the three centres. Once diagnosed with MPS IVa patients will be managed according to one of the following treatment pathways:

(1) Palliative Care – a very small number of families choose not to undergo surgical/medical treatment and receive supportive care only. Such patients would be expected to become tetraparetic in late childhood and life expectancy is reduced to the teens/very early adulthood due to progressive cardiorespiratory disease and the complications of severe physical disability.

(2) Treatment with Elosulfase Alfa and Surgeries – most families in our experience have chosen to take up treatment with elosulfase alfa and are then managed according to the Managed Access Agreement. This will involve receiving weekly enzyme replacement therapy, initially in hospital but then quickly in the home/school setting initially using the services of a homecare nursing company. Increasingly families are being encouraged to become independent in managing the infusions and become less reliant on homecare nurses. For children, treatment usually involves the placing of a totally implanted vascular access device due to the difficulties obtaining weekly peripheral IV access. Patients undertaking treatment with elosulfase alfa also agree to undertake any necessary surgical intervention needed to maintain quality of life (and thereby benefit of ERT) including spinal surgery (cervical and thoracolumbar), knee surgery (hemiepiphysiodesis for genu valgum), ENT surgery (frequently grommets/T-tubes, hearing aid assessments and adenotonsillectomy) and cardiac surgery (especially heart valve).

(3) Non-ERT management – a minority of families have chosen not to take up treatment with elosulfase alfa or have been deemed too advanced in their disease course to obtain reasonable benefit from the treatment. In our experience only 2

patients were deemed ineligible for the MAA whereas 5 patients elected not to commence the MAA after participating in lengthy clinical trials of elosulfase alfa. These patients are followed up in the service at less frequent intervals than those receiving ERT, but on the whole have the same assessments and organ-directed supportive management as required. Surgical intervention is offered in the same way as those receiving ERT but with additional consideration of the likely long term benefit in the context of a progressive disorder.

There are no alternative disease-modifying therapies available. Haematopoietic stem cell transplantation is not widely considered an effective modality for this lysosomal storage disorder which predominantly affects the musculoskeletal system and gene therapies are at present and is not recommended (due to lack of evidence) in the recently published international consensus-based recommendations:

Akyol, M.U., Alden, T.D., Amartino, H. *et al.* Recommendations for the management of MPS IVA: systematic evidence- and consensus-based guidance. *Orphanet J Rare Dis***14,** 137 (2019). https://doi.org/10.1186/s13023-019-1074-9

These guidelines are relevant and developed through a robust Delphi-based approach with disease specialists from multiple centres across the world. The recommendations, though mostly based on Grade D evidence, do achieve a high level of consensus (90-100%) and are broadly in agreement with practice in the NHS England approved clinical centres.

In the West Midlands there is a high incidence of patients with MPS IVa who are homozygous for a G116V mutation in *GALNS* which has been reported to be associated with a more severe phenotype at presentation and more rapid progression of skeletal deformity (see SSIEM 2014 Annual Symposium: Abstracts. *J Inherit Metab Dis* **37,** 27–185 (2014). https://doi.org/10.1007/s10545-014-9740-5) 85% of the patients treated at this centre are of Pakistani ethnicity and 70% of those patients share this genotype. Whilst a number of these patients contributed to the clinical trials of elosulfase alfa, these studies were not powered sufficiently to detect a difference in the capacity of this subgroup of patients to benefit from this treatment but they may represent a distinct severe subgroup whose disease course may be modified to a different extent by elosulfase alfa.

Should the technology be funded, there would be no immediate risk to the delivery of the highly specialised service for paediatric lysosomal storage disorders. Patients are currently being treated and there is no reason to expect a surge in demand for treatment after a positive decision. In our experience, patients who meet the MAA criteria in 2019/20 have elected to start treatment even if this is only for a short time. However our centre, and possibly others, has found the delivery of the MAA has placed a burden on the infrastructure of the team, particularly in terms of allied health professional time for arranging regular assessments (notably physiotherapy and pulmonary function testing). In the longer term, some centres may find they need to invest in additional staffing to meet these requirements, although many of these requirements are recommended in patients regardless of whether they are treated with ERT or not.

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Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

The advantages and disadvantages of the technology

The focus of this review should be the "unanswered questions" from the original review, namely how elosulfase alfa performed in "real world" use outside of a clinical trial and particularly in a range of patients who had not been included in the main clinical trials. For paediatrics, this includes children under the age of 5yrs who were excluded from the MOR-004/MOR-005 trial (and only a small number were examined in a separate substudy MOR-007).

From our experience it is important to state from the outset that no patient at this centre who commenced treatment with elosulfase alfa on the managed access agreement, had to stop treatment due to non-achievement of more than one of the five annual outcome criteria. All our patients were motivated to continue treatment (as evidence by their agreement to stick to the rigid requirement to miss no more than 3 infusions for non-clinical reasons in 14 months) which in itself suggests that patients and families were perceiving benefit from treatment.

At this centre, six patients who took part on clinical trials of elosulfase alfa elected not to continue treatment on the managed access agreement, and this represents the only patients in this centre in whom elosulfase alfa treatment was "stopped". Four of these six patients were homozygous for the severe G116V mutation. Three of these patients (and one non-G116V patient) had suffered a significant and acute deterioration in mobility as a consequence of advanced skeletal disease already evident prior to commencement of elosulfase alfa treatment and in three cases this was as a consequence of necessary surgical intervention. Only two patients elected not to continue onto the MAA due to the treatment burden, and in both cases their disease was advanced prior to starting treatment. Their experience therefore does not negate the potential of elosulfase alfa to positively impact the disease course of MPS IVa in all patients if commenced early.

Our experience of the managed access agreement for elosulfase alfa therefore includes two cohorts:

Cohort 1: four older patients who had been treated on the clinical trials, perceived ongoing benefit and continued to longer term treatment on the MAA. Treatment for these patients will have been for between 8 and 11 years.

Cohort 2: eight patients who commenced elosulfase alfa on the MAA only. These patients will have been treated for up to 5 years and on average are younger patients at commencement of ERT than in the clinical trials. Seven of these patients were under 5yrs of age at commencement of treatment. Seven of these eight patients were homozygous for the severe G116V mutation.

All patients, regardless of age and severity, demonstrated a significant reduction in urinary Keratan sulphate excretion, including those in whom a rise in anti-elosulfase alfa antibodies was detected on treatment. This is in keeping with the results of the clinical trials and indicates a positive biological effect in all patients which is an

essential pre-requisite for any disease-modifying therapy. However this measure does not give any indication of the clinical significance of the impact of treatment on disease course.

Treatment was well tolerated by all patients. Infusion-associated reactions were rare and when they did occur were easily managed with conventional premedications. No unexpected adverse events attributable to the therapy alone were noted in our patients. Complications of venous access devices were no more frequent or challenging than in any other lysosomal storage disorder for which enzyme replacement therapy is approved.

All patients in Cohort 1 continued treatment with the MAA. Two patients (both homozygous for G116V) did demonstrate a reduction in mobility (as evidenced by a reduced six minute walk test [6MWT] distance compared to baseline) however continued to demonstrate stability/improvement of cardiac and pulmonary function and quality of life scores. There is no valid control group to compare these patients' outcome with. Untreated patients cannot be considered a valid control group as they contain predominantly a cohort of patients deemed too severe to consider treatment in the first place. These patients have been on treatment for between 8 and 11 years and the ongoing stability of cardiac and lung disease is encouraging. The reduction in mobility over a longer period of time in the patients homozygous for G116V may be in keeping with the more severe skeletal phenotype of these patients and may suggest that these patients may not continue to see benefit in some areas in the long term when treatment is started with already advanced disease.

As paediatric metabolic specialists, our scientific interest was particularly focussed on Cohort 2 as these are the patients who potentially have the most to gain from elosulfase alfa and were a group who were not extensively studied in the clinical trials. The managed access agreement allowed us to observe treatment effect in a reasonable number (though still numerically small given the rarity of the condition) of children under the age of 5yrs diagnosed with the severe G116V mutation. Respiratory function testing is not so relevant to assessing these patients as many of them are too young to be able to perform lung function assessments adequately (and the untreated natural history at this age would be towards improvement as the chest grows with age initially). Cardiac function testing is also less relevant an assessment as it is not typical to see clinically significant cardiac disease due to MPS IVa at this age. An improvement in mobility was noted in all patients in this cohort who have had repeated assessments – however again the relevance of this finding is questionable as young children naturally progress with walking up until skeletal disease takes its toll. Less than five years of treatment is not long enough to assess these patients' long term outcomes with respect to mobility. Quality of life scores/parent reported outcomes were positive in this group and remained consistently so. Families report that children demonstrated increased energy particularly in the days after their infusion. They remain active and playful and are attending mainstream education placements where appropriate for their age. Formal neuropsychological measurements of development have not been performed in these patients, but in our experience mainstream education has been the norm for the majority of patients.

We have monitored growth in Cohort 2 and though the number of data points is small, there does not appear to be a significant difference in height z-score over time compared with the natural history data which is published in the MOR-CAP data. (Harmatz P, Mengel KE, Giugliani R *et al.* The Morquio A Clinical Assessment Program: Baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects. *Mol Genet Metab* ***109(1),*** 54-61 (2013). https://doi.org/10.1016/j.ymgme.2013.01.021)

There is an expected decrease in height z-score over time which is evident as these patients deviate further from the average height of their age-matched peers from -2.09 between 0-4yrs to -5.00 between 5-11 years. Our (unpublished – but hopefully to be presented at SSIEM 2020, Freiburg) data show that in G116V homozygous children started on elosulfase alfa before the age of 5yrs, the rate of decline in height z-score remains the same as that reported in the MOR-CAP cohort with the cross-sectional height z-scores showing the same trend between 2 and 8 years of age. The published results of the MOR-007substudy (which was not powered to detect significant differences) showed no significant difference in height z-score compared to MOR-CAP over 52 weeks but suggested a trend that the rate of decline was slower in this group (Jones SA, Bialer M, Parini R *et al* Safety and clinical activity of elosulfase alfa in pediatric patients with Morquio A syndrome (mucopolysaccharidosis IVA) less than 5 y. *Pediatr Res* 2015 Dec; 78(6): 717–722 https://doi.org/10.1038/pr.2015.169) This would support the view that patients homozygous for the G116V mutation have a particularly severe skeletal phenotype that responds less well to elosulfase alfa therapy and may limit the long term benefit expected in these patients as they grow older – however the five year managed access agreement period is insufficient to conclude this with any certainty.

The treatment, despite its intensiveness, has been well accepted by patients and families. In particular a sizeable number of families (about half the total cohort) have become independent infusers of the treatment and not reliant on inpatient medical facilities nor the services of a homecare nursing service. At our centre the six monthly assessments required by the MAA have been able to fit easily into the multidisciplinary LSD clinics we run and the assessments have often been possible to arrange in a single clinic visit. This makes the clinic visit a long day but the families have generally found this acceptable to reduce the burden of frequent hospital visits.

Families have accepted the need for formal stopping criteria and the stringent compliance requirements of the managed access agreement. If this were to be rolled out for a longer period, it should be noted that the requirement to miss no more than 3 infusions in 14 months is a strict and restricting requirement. It has the potential to limit overseas travel which is relevant to a patient group with a high proportion of ethnic minority backgrounds for whom the ability to take longer trips overseas is important. It has also restricted older patients from participating in longer overseas travel for educational purposes. It is also considerably stricter than the rules applied to any of the existing funded enzyme replacement therapies.

Whilst our experience with patients homozygous for the G116V mutation suggests that these may be a group with a suboptimal response to elosulfase alfa treatment,

this cannot be concluded yet with certainty. This will become apparent only with longer term treatment of patients commenced at younger ages. However if the stopping criteria used in the managed access agreement continue to be applied after a positive recommendation, then I would expect these patients would naturally end up stopping treatment if their skeletal disease is not impacted positively. At present I cannot say that they should be identified as a subgroup of patients who should not receive therapy – but with longer observation of early treated patients this may become apparent. These patients do, however, still report benefits outside the musculoskeletal system. We recognise, however, that there is the potential that the benefits of elosulfase alfa therapy on patients who do not have the G116V mutation may be underestimated by clinical trials and registry data which report combined outcomes and therefore any further long term evaluation of outcomes should prospectively consider these patients separately.

Patients treated with elosulfase alfa have not shown a reduced need for additional therapies such as surgeries. This was never intended to be the case, and indeed the more frequent and careful follow-up of patients mandated by the managed access agreement has arguably led to earlier and more pro-active referrals for relevant surgical procedures. We have anecdotal reports only of the results of such operations being more successful in patients on treatment with elosulfase alfa – in particular the success of hemiepiphysiodesis in correcting genu valgum appears to be notable in patients receiving elosulfase alfa compared to historic cases – however this has not been formally studied. Improvements in cardiorespiratory disease may make bigger operations such as spinal interventions safer also. The lack of a reduction in surgical intervention should not be perceived as a lack of benefit however – conversely centres may be considering more aggressive surgical interventions (such as tracheal reconstruction) now in patients whose quality of life may be enhanced by enzyme replacement therapy.

Any additional sources of evidence

Since 2015 there have been a number of relevant publications on the role of elosulfase alfa, the real-world application in other countries and outcomes in areas not well described in the pivotal studies (such as patient reported outcomes).

The majority of our patients (and many patients in England) have been recruited to the Morquio A Registry Study though I am not aware that there has yet been a formal publication of the data in this registry. The registry is funded by BioMarin Pharmaceutical Inc and unpublished data may well form part of the commercial submission.

Unpublished growth data from our own cohort is included above.

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Highly Specialised Technology Evaluation

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

Implementation issues

Implementation of a positive recommendation would not be challenging for this or any other paediatric centre. It would simply formalise existing arrangements which have developed from the managed access agreement. At our centre, the requirements of the MAA have been incorporated into standard clinical care and we would foresee no difficulties with continuing this. We are not aware of any patients who are not currently receiving elosulfase alfa but who would ask to do so if a positive recommendation were made so would not be expecting a surge in demand for therapy.

Equality

I do not think this evaluation would automatically exclude any population protected by equality legislation. Patients already very severely physically disabled (eg non-walking) were still entitled to treatment on the MAA although benefits then had to be demonstrated in the 25ft ambulation test rather than the 6MWT. There is the potential that patients who are completely non-ambulant may still benefit from treatment in other areas however generally in MPS IVa complete loss of ambulation is also associated with endstage cardiorespiratory impairment and therefore such patients would not be expected to gain significantly from treatment. However any recommendation wording should be careful to address clinical categories rather than excluding non-ambulant persons per se – and the evaluation should take note of the experiences from centres who have treated patients unable to complete 6MWT assessments.

Likewise the possibility that patients homozygous for the G116V mutation may fall into a group of less responsive patients will affect one ethnic minority as this mutation is exclusively seen in patients of Pakistani origin. However this can be mitigated by having firm clinical stopping criteria which are independent of genotype.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Appendix D - professional organisation statement template

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Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2)

HST Report

Source of funding

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Report reference:	Edwards SJ, Wakefield V, Bacelar M, Barton S, and Roberts S. Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2): A Highly Specialised Technology Appraisal. BMJ Technology Assessment Group, 2021.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the clinical sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Sarah Roberts	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

3MSCT	3-minute stair climb test
6MWT	6-minute walk test
APPT	Adolescent Pediatric Pain Tool
BPI	Brief Pain Inventory
CS	Company submission
CSR	Clinical Study Report
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
ESA	Elosulfase alfa
EQ-5D	EuroQol 5 dimensions, 5 levels
FEV1	Forced expiratory volume in 1 second
FIVC	Forced inspiratory vital capacity
FVC	Forced vital capacity
HSCT	Haematopoietic stem cell transplant
HST	Highly Specialised Technology
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
IV	Intravenous
LVEF	Left ventricular ejection fraction
MAA	Managed Access Agreement
MARS	Morquio A Registry Study
MPP	Modified per protocol
MPS IVA	Mucopolysaccharidosis type IVA
MPS-HAQ	MPS Health Assessment Questionnaire
MVV	Maximal voluntary ventilation
NICE	National Institute of Health and Care Excellence

PRO	Patient-reported outcome
PSM	Propensity score matching
QALY	Quality-adjusted life year
QOW	Every other week
QW	Weekly
RCT	Randomised control trial
SD	Standard deviation
SLR	Systematic literature review
SoC	Standard of care
uKS	Urinary keratan sulfate

1 Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that are likely to have the greatest effect on the incremental cost effectiveness ratio (ICER). Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main body of the ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1 provides a summary of the ERG's key issues.

Table 1. Summary of key issues

Issue number	Summary of issue	Report sections
Issue 1	Lack of robust comparative data for ESA compared to SoC and the heterogeneity of MPS IVA	2.3 and 3
Issue 2	Use of ESA treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation in some of the ex-trial MAA patients	2.3.2 and 3.2.3
Issue 3	Absence of an SLR to identify studies for SoC	3.1
Issue 4	Clinical heterogeneity in the clinical analyses and inappropriate methods for handling of missing data	3.2, 3.3 and 3.5
Issue 5	Use of inconsistent timepoints within and between studies for assessment of clinical outcome data	3.2, 3.3 and 3.5
Issue 6	Clinical data used in the model: The data included in the economic model are unfit for decision making.	3.8

Issue 7	Modelling approach: The use of a WC-based model is unlikely to capture the impact of ESA on patients' disease and the thresholds for change in WC use in the model are contradictory to the underlying clinical data.	4.2.4.1
Issue 8	Estimation of WC dependency in the model: Given the availability of annual WC use data, it is unclear to the ERG why these were not used by the company. The ERG disagrees with the company's assumptions of constant decline in the SoC arm and the company's assumption that after year 1 in the model, only [redacted]% of ESA patients progress to the next (more dependent) WC state in the model.	4.2.6.2
Issue 9	Mortality: The company's approach to estimating mortality is overestimating survival in the model.	4.2.6.4
Issue 10	Estimation of quality of life in the model: The company's justification for having treatment-specific utility values by WC category is inconsistent with the company's justification for having a WC based model and it double counts the benefits associated with ESA.	4.2.8.1
Issue 11	ESA costs: The company underestimated the treatment costs in the analysis.	4.2.9.1

Abbreviations: ERG, Evidence Review Group; ESA, elosulfase alfa; MAA, managed access agreement; MPS IVA, mucopolysaccharidosis type IVA; QW, weekly; SoC, standard of care; SLR, systematic literature review; WC, wheelchair.

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the clinical data used to populate the economic model; the modelling approach; and the assumptions around the benefits associated with elosulfase alfa (ESA).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled by the company to affect QALYs by:

- Generating a survival benefit compared to standard of care (SoC);
- Preventing patients from increasing their wheelchair (WC) dependency;
- Increasing patients' quality of life through improvements in 6-minute walk test (6MWT) and forced vital capacity (FVC) outcomes compared to SoC;
- Increasing patients' quality of life through treatment when compared to SoC (ESA patients were assumed to have higher utility values than SoC patients for the same health state);
- Reducing the burden on carers' disutility when compared to SoC;
- Decreasing patients' recovery time from surgery;
- Postponing patients' need for surgery.

Overall, the technology is modelled by the company to affect costs by:

- Its higher costs compared with SoC;
- Its lower carer costs compared with SoC;
- Preventing patients from increasing their WC dependency, associated with higher costs in the model.

The ERG's preliminary assessment of the modelling assumptions likely to have the greatest effect on the ICER are:

- The assumption that [redacted]% of ESA patients do not have disease progression after year 1 in the model;
- The proportion of patients allocated to each WC state at baseline and at the end of year 1 in the model (given that the movement of ESA patients across WC categories is minimal after year 1);
- The assumption that patients on ESA experience higher utility values than SoC patients in the no WC; sometimes WC; WC-dependent and paraplegic health states;
- The baseline weight distribution in each WC category;
- Carers costs are the key driver of SoC costs in the model, amounting to 96% of total costs for the comparator arm.

1.3 The decision problem: summary of the ERG's key issues

Table 2 and Table 3 present the ERG's key issues relating to the decision problem.

Table 2. Issue 1: Lack of robust comparative data for ESA compared to SoC and the heterogeneity of MPS IVA

Report section	2.3 and 3
Description of issue and why the ERG has identified it as important	The key data for ESA and SoC originate from the MAA, MOR-005 and MOR-001 non-randomised studies. These data are mainly utilised in naïve comparisons, which the ERG considers to be flawed because of the underlying heterogeneity in the disease presentation of patients with MPS IVA. In addition, the ERG is concerned about the reliability of the results reported for ESA and SoC as detailed further in Issues 3 to 5. The ERG is also concerned with the data used in the PSMs for 6MWT provided by the company in their response to clarification questions. The ERG therefore considers there is a lack of robust comparative data for ESA compared to SoC in the CS.
What alternative approach has the ERG suggested?	The ERG considers a complete case analysis for patients in each of the studies would be more appropriate. The use of a PSM analysis for the patients following complete case analysis could then be explored to attempt to account for differences at baseline between patients in the ESA and SoC treatment groups.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, however the ERG notes that this is likely to be a key driver of the economic results.
What additional evidence or analyses might help to resolve this key issue?	Ideally an analysis comparing the full ITT population of MOR-005 QW-QW and the patients from MorCAP1 should be conducted and a further analysis of the patients from the MAA and the full MOR-001 population. In both instances, complete case analyses should be conducted and then the feasibility of a subsequent PSM analyses should be explored.

Abbreviations: 6MWT, 6-minute walk test; CS, company submission; ERG, Evidence Review Group; ESA, elosulfase alfa; ITT, intention to treat; MAA, managed access agreement; MPS IVA, mucopolysaccharidosis type IVA; PSM, propensity score matching; QW, weekly; SoC, standard of care; WC, wheelchair.

Table 3. Issue 2: Use of ESA treatment regimens that are not consistent with the recommended 2.0 mg/kg/QW dose at treatment initiation in some of the ex-trial MAA patients

Report section	2.3.2 and 3.2.3
Description of issue and why the ERG has identified it as important	The ERG notes that some patients ([redacted]) in the Ex-Trial cohort of the MAA received ESA treatment regimens in their original clinical trials prior to enrolment in the MAA that are not consistent with the 2.0 mg/kg/QW dose approved in the marketing authorisation. The current analyses of the data from these patients uses their baseline from the start of their original clinical trial and the ERG considers this to potentially impact on the reliability of the results from the Ex-Trial cohort of the MAA.
What alternative approach has the ERG suggested?	The ERG considers that a sensitivity analysis including only patients who have consistently received the recommended 2.0 mg/kg/QW dose of ESA from ESA treatment initiation should be conducted for the MAA to explore the impact of the inclusion of patients who have received alternative doses.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, but changes in the clinical efficacy for ESA will impact the economic results.
What additional evidence or analyses might help to resolve this key issue?	As discussed above, a sensitivity analysis to check the consistency of the MAA results if only patients who have received the recommended 2.0 mg/kg/QW dose of ESA from ESA treatment initiation are included would be beneficial.

Abbreviations: ERG, Evidence Review Group; ESA, elosulfase alfa; MAA, managed access agreement; MPS IVA, mucopolysaccharidosis type IVA; PSM, propensity score matching; QW, weekly.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Table 4 to Table 6 present the ERG's key issues with the company's clinical-effectiveness evidence.

Table 4. Issue 3: Absence of an SLR to identify studies for SoC

Report section	3.1
Description of issue and why the ERG has identified it as important	The company did not report details of how the MOR-001 study was identified and selected as the best source of data to inform SoC in the submission. The ERG is therefore concerned about the robustness of the company's methods for selecting MOR-001 and cannot be certain as to whether alternative more appropriate sources of data have been omitted.
What alternative approach has the ERG suggested?	The ERG considers a full SLR to search for data on SoC is required to confirm that MOR-001 has been appropriately included as the only source of data for SoC.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, however the ERG notes that changes to the source of data for SoC is likely to be a key driver of the economic results.
What additional evidence or analyses might help to resolve this key issue?	A full SLR to identify studies of SoC in MPS IVA is required.

Abbreviations: ERG, Evidence Review Group; MPS IVA, mucopolysaccharidosis type IVA; SLR, systematic literature review; SoC, standard of care.

Table 5. Issue 4: Clinical heterogeneity in the clinical analyses and inappropriate methods for handling of missing data

Report section	3.2, 3.3 and 3.5
Description of issue and why the ERG has identified it as important	The ERG notes from clinical expert advice that MPS IVA comprises a heterogenous patient population and is thus concerned that individual patients could have markedly different baselines and treatment responses. The company's approach of comparing the mean estimates of patients observed at each time point, does not account for the fact that these represent different cohorts of patients with potentially very different outcomes.
What alternative approach has the ERG suggested?	Due to the heterogeneity and potentially large impact missing data could have on the clinical analyses, the ERG considers a complete case analysis is required.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, however the ERG notes that this is likely to be a key driver of the economic results.
What additional evidence or analyses might help to resolve this key issue?	As discussed for Issue 1, the ERG considers a complete case analysis for patients in the each of the MOR-001 (including for MorCAP1), MAA and MOR-005 QW-QW studies is required to ensure the clinical data are from a consistent cohort of patients.

Abbreviations: ERG, Evidence Review Group; MPS IVA, mucopolysaccharidosis type IVA; QW, weekly.

Table 6. Issue 5: Use of inconsistent timepoints within and between studies for assessment of clinical outcome data

Report section	3.2, 3.3 and 3.5
Description of issue and why the ERG has identified it as important	The ERG notes that inconsistent timeframes have been used to inform the clinical analyses at set timepoints (Year 1, Year 2, Year 3 etc.) presented by the company. In particular, for MOR-001, the ERG notes that the data used to inform the Year 1 change from baseline could have been collected up to three years after the baseline visit. In addition, the ERG considers the company may have used inappropriate methods to assign data to timepoints. For example, the IPD supplied to the ERG [redacted].
What alternative approach has the ERG suggested?	The ERG considers a consistent approach to defining timepoints in the clinical analyses are required.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, however the ERG notes that this is likely to be a key driver of the economic results.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers the clinical data should be re-analysed to ensure consistent methods are used to assign clinical data to analyses at different timepoints. For example, data from only 0.5 to <1.5 years post-baseline should be used to inform the 1 year change from baseline analysis.

Abbreviations: ERG, Evidence Review Group; IPD, individual patient data; MAA, managed access agreement.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Table 7 to Table 12 present the ERG's key issues with the company's cost-effectiveness analysis.

Table 7. Issue 6 Clinical data used in the model

Report section	3.8
Description of issue and why the ERG has identified it as important	The data included in the economic model are unfit for decision making. Please see Sections 1.3 and 1.4 for more details.
What alternative approach has the ERG suggested?	The ERG considers that the appropriate set of data to estimate the relative treatment effect of ESA against SoC relies on the complete case analysis of the MorCAP1 data matched to the MOR-005 population, and the complete case analysis of the MOR-005 QW-QW population.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, however the ERG notes that this is likely to be a key driver of the economic results.
What additional evidence or analyses might help to	A complete case analysis comparing the full ITT population of MOR-005 QW-QW and the patients from MorCAP1 should be conducted and then the feasibility of subsequent PSM analyses for each outcome should be

resolve this key issue?	explored. The results from these analyses should be used in the economic model for both ESA and SoC.

Abbreviations: ERG, Evidence Review Group; ESA: elosulfase alfa; ITT, intention to treat; PSM: propensity score matching; QW, weekly.

Table 8. Issue 7 Company's modelling approach

Report section	4.2.4.1
Description of issue and why the ERG has identified it as important	Use of a WC-based model. Endurance (measured through 6MWT) and pulmonary outcomes (measured through FVC) have been deemed the most relevant and sensitive outcomes in MPS IVA by: patients; clinical experts; and the HST2 committee, to assess disease progression and quality of life. However, 6MWT and FVC outcomes in the MAA have been found by the company to be poor predictors or poorly correlated with changes in WC use. Based on that observation, the company decided to use WC use as the main modelling outcome. The ERG disagrees with the company's conclusion and notes that making WC use the key outcome in the economic analysis is unlikely to capture the impact of ESA on patients' disease. The ERG also concluded that there is evidence to support a strong correlation between endurance and mobility measures (6MWT) and patients' respiratory measures (FVC) with patient's EQ-5D-5L/HRQoL. Furthermore, the thresholds for change in WC use defined by the company in the model are contradictory to the clinical data observed at baseline in the MAA dataset.
What alternative approach has the ERG suggested?	The ERG considers that a model based around endurance and respiratory measures would have provided a better tool for decision making. Crucially, such a modelling approach would have allowed the company to use the MAA or the MOR-005, and MOR-001/MorCAP1 data to estimate the decrease (or increase) in 6MWT and FVC outcomes according to treatment arm, instead of relying almost solely on assumptions around disease progression.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, however the ERG notes that this is likely to be a key driver of the economic results.
What additional evidence or analyses might help to resolve this key issue?	If a WC-based model is to be maintained, the ERG recommendation is that more WC, 6MWT, and FVC data from MorCAP1 and MOR-005 are incorporated in the model and crucially, that the WC data collected from the ESA and comparator studies are consistent and comparable (see Table 9). Furthermore, the ERG notes that the thresholds defined for changes in WC states in the model should be representative of the underlying clinical data. Equally, the ERG notes that it has not seen any data to substantiate the company's assumption that ESA patients do not progress after year 1 in the model. This assumption is one of the key drivers of the company's base case economic results and, therefore, the ERG requests that the company ensures that any long-term assumptions of treatment effectiveness made in the model are consistent with the underlying clinical data.

Abbreviations: 6MWT, 6-minute walk test; CS, company submission; ERG, Evidence Review Group; ESA, elosulfase alfa;

FVC, forced vital capacity; HRQoL, health-related quality of life; ITT, intention to treat; MAA, managed access agreement; WC, wheelchair.

Table 9. Issue 8 Estimation of WC dependency in the model

Report section	4.2.6.2
Description of issue and why the ERG has identified it as important	The ERG disagrees with the company's method for estimating transition probabilities across the WC states in the model. Given the availability of annual WC use data, it is unclear to the ERG why the data used to model transitions in the first year of the model was based on the WC change from baseline to 72 weeks in the MAA dataset and from baseline to 2 years in the MOR-001 study, respectively. The ERG has several concerns around the estimates used to derive the increase in WC dependency for SoC patients in the following years of the model, through the use of 6MWT and FVC outcomes. The company assumed an annual 0.1L decline in FVC for SoC patients based on clinical expert opinion. Nonetheless, the Harmatz *et al*. 2013 study reported an increase in patients' FVC over the period of the study of 2.44% in total FVC (L) per year (ITT population) and of 2.39% for the MOR-005 matched population. The company did not provide a justification for using the 6MWT decline for SoC patients from the Harmatz *et al*. 2013, while ignoring the increase in FVC for the same patients in the study. Without a robust clinical justification for the company's decision, the ERG does not agree the company's approach as it is biased in favour of ESA. Furthermore, the ERG disagrees with the company's assumption that after year 1 in the model, only [redacted] of ESA patients progress to the next (more dependent) WC state in the model, per year. The ERG's preliminary investigation of the MAA and MOR-005 data did not substantiate this assumption, and has shown that for ESA patients, WC dependency could still worsen, stabilise, or improve at year 3, therefore, contradicting the company's assumption that ESA patients have a stable WC use from year 1 until they die in the model.
What alternative approach has the ERG suggested?	The ERG recommends that the WC data used in the first year of the model is the annual probability of patients going from their baseline WC state to their respective WC state at the end of year 1, in both MorCAP1 and MOR-005 (derived from a complete case analysis); The ERG recommends that the company uses the WC annual data (year 1 to year 2; and year 2 to year 3, if possible) available from MorCAP1 and from MOR-005 to estimate transition probabilities between the NWC, SWC, and WCD states in the model for the first 2 or 3 years; In the following years, and in order to estimate changes in WC dependency in the model, the ERG recommends that the values used to estimate the change in 6MWT and FVC outcomes for SoC and ESA patients are taken from the re-analysis of the MorCAP1 and MOR-005, respectively, and that the values used are based on the available annual estimates. The ERG also recommends that the entrance and exit thresholds for WC states are re-analysed and made consistent with the underlying clinical data (as discussed in Issue 7).

What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, however the ERG notes that this is likely to be a key driver of the economic results.
What additional evidence or analyses might help to resolve this key issue?	The ERG recommends that the company provides the re-analysed IPD for WC change, annual 6MWT and FVC to be incorporated in the updated model to the ERG, for validation. The ERG recommends that once the MOR-005 and the MorCAP1 data have been re-analysed, the company conducts a comparison of the annual values for 6MWT and FVC outcomes in both studies and assesses if additional scenario analyses should be conducted. For example, if the data signals thar ESA might not have a benefit against SoC for NWC patients (as seen in the ERG's preliminary analysis), the ERG recommends including a scenario in the model where ESA does not have a benefit against SoC for NWC patients.

Abbreviations: 6MWT: 6-minute walking test; ESA: elosulfase alpha; FVC: forced vital capacity; IPD: individual patient-level data; MAA: managed access agreement; NWC: no wheelchair; SWC: sometimes wheelchair; WCD: wheelchair dependent.

Table 10. Issue 9 Estimation of mortality

Report section	4.2.6.4
Description of issue and why the ERG has identified it as important	The ERG disagrees with the company's base case approach to estimating mortality and considers survival to be overestimated in the model. Clinical expert opinion provided to the ERG informed that for a mild form of MPS IVA, patients on treatment could live to be around 50 or 60 years old. However, there are [redacted]% of ESA patients alive at 93 years old in the model. This suggests a clinically implausible scenario and an overestimation of survival in the model. The ERG's clinical experts also disagreed with the company's assumptions that ESA patients experience the same mortality as the general population matched for age and gender. This was considered clinically implausible as many of the complications of MPS IV that cause death are not normalised by ESA, such as cardiac valvular disease, cervical spinal compromise, chest deformities (which cause restrictive lung disease), and tracheal obstruction.
What alternative approach has the ERG suggested?	The ERG recommends that the company uses the approach employed in their scenario analysis where mortality is linked to FVC decrements as their base case analysis, with the following alternations/corrections: • The ERG recommends that the company uses the improvement in FVC over time observed in MOR-005 (re-analysed) instead of MOR-001/002 to estimate the impact of ESA on mortality, and the FVC data from MorCAP1 (re-analysed) to estimate mortality in the SoC arm; • The ERG considers that the RR of 1.12 used by the company for every 10% decrement in FVC is incorrectly used, and instead recommends that the company applies the 1.15 rate ratio from Neas and Schwartz, 1988 study and applies it correctly to the general population mortality (i.e. by exponentiation and not multiplication).

What is the expected effect on the cost-effectiveness estimates?	Not possible to predict.
What additional evidence or analyses might help to resolve this key issue?	If the company decides to keep their base case approach to modelling mortality in the model, the ERG suggests that instead of using the RR observed in Quartel *el al*. 2018 and applying it to the general population mortality, the company should use the 15-year Kaplan-Meier survival data observed for ERT-treated and SoC patients in the same study in their analysis.

Abbreviations: 6MWT, 6-minute walk test; ERG, Evidence Review Group; ERT, enzyme-replacement therapy; MPS IVA, mucopolysaccharidosis type IVA.

Table 11. Issue 10 Estimation of quality of life in the model

Report section	4.2.8.1
Description of issue and why the ERG has identified it as important	The ERG disagrees with the company's estimation of quality of life in the model. The ERG notes that the company's justification for having treatment-specific utility values by WC category is inconsistent with the company's justification for having a WC based model. If, as the company suggests, WC use is the most appropriate measure for capturing the change in patients' quality of life, then the impact of ESA on patients' WC change should be enough the capture the change in patients' quality of life. Furthermore, using different utility values per treatment arm in the same WC state, combined with the utility increments estimated for FVC and 6MWT gains in the ESA arm, double counts the benefits associated with the drug in the analysis. Given the ERG's view that the WC categories used by the company are not appropriate to capture the benefit of ESA, the ERG's preference is to assume that all WC states have the same utility in the model, and apply utility increments associated with gains in the 6MWT and FVC outcomes observed for ESA. Furthermore, given the issues found in the IPD on quality of life for MAA patients, the ERG's preference is that utility estimates from the original company submission for the HST2 (which in turn were taken from the Hendriksz *et al.* 2014 burden of disease study for patients with MPS IVA) are used.
What alternative approach has the ERG suggested?	The ERG recommends that the company uses the same utilities values from the HST2; that all WC states have the same utility in both treatment arms, and utility increments associated with gains in the 6MWT and FVC outcomes observed for ESA are estimated; and finally, that the FVC and 6MWT increments used are those underpinning the treatment effectiveness analysis and the clinical data used in the model.
What is the expected effect on the cost-effectiveness estimates?	Not possible to predict, but this is likely to be a key driver of the economic results.
What additional evidence or analyses might help to	The ERG remains unclear as to how the company estimated the mean gain in 6MWT in the ESA arm (60m) and increase in mean FVC (0.054L) to derive utility increments. If the company decides to use these gains in their

resolve this key issue?	updated base case analysis, the ERG recommends that a clear explanation on the sources used, and the calculations and assumptions undertaken are provided. Given the likely uncertainty around the FVC and 6MWT benefits associated with ESA resulting from the comparison of MorCAP1 and MOR-005 data, the ERG also recommends an exploratory analysis where no utility increments are assumed for ESA. In this scenario, patients' gain in quality of life comes from changes in WC use, and the movement across these states in both treatment arms

Abbreviations: 6MWT, 6-minute walk test; ERG, Evidence Review Group; ESA, elosulfase alfa; ITT, intention to treat; MAA, managed access agreement; MPS IVA, mucopolysaccharidosis type IVA; SoC, standard of care; WC, wheelchair.

Table 12. Issue 11 Underestimation of treatment costs in the analysis

Report section	4.2.9.1
Description of issue and why the ERG has identified it as important	The ERG's preliminary investigation of the IPD concluded that the company underestimated the cost of ESA in the model. As the company used the average weight of patients in each WC state and patients were not evenly distributed across the WC categories at baseline (5% asymptomatic, 40% NWC, 50% SWC, and 5% WCD), the weighted average of patients' weight at the beginning of the model was lower than the average weight observed in the MAA population. Given that the movement of ESA patients across WC categories is reduced throughout the model, the baseline weight distribution in each WC category is one of the key model drivers. Equally, the proportion of patients allocated to each WC state at baseline and at the end of year 1 in the model are also key drivers of the economic results. Furthermore, the company included a 20% discount for ESA in their base case based on an assumption that VAT would not apply to home infusion drugs. This was previously removed in the original ERG report for the HST2 as according to the NICE methods guide, VAT should be excluded from all economic evaluations, therefore there would be no difference between the drug cost between home and hospital care.
What alternative approach has the ERG suggested?	If the MAA data were to be analysed with a complete case analysis approach, the baseline weight per WC category is likely to change. Changing the method of analysis for the clinical data might also influence the outcome around weight change throughout the MAA period. Nonetheless, given the ERG's consideration that MOR-005 is a more robust source of evidence to estimate ESA's effectiveness, the ERG recommends that the weight data used to estimate treatment costs in the model is sourced from MOR-005. Additionally, the ERG cautions the company to adjust the weight of patients in every model cycle in order to satisfy the average number of vials used in MOR-005 (or in the MAA if the company does not change the source for weight data in the model). The ERG recommends that the company removes the 20% discount from its base case results.
What is the expected effect on the cost-effectiveness	It is expected that the costs associated with treatment with ESA will increase in the model.

estimates?	
What additional evidence or analyses might help to resolve this key issue?	The availability of IPD for baseline and follow-up weight in MOR-005 and the MAA.

Abbreviations: 6MWT, 6-minute walk test; CS, company submission; ERG, Evidence Review Group; ESA, elosulfase alfa; IPD, individual patient data; ITT, intention to treat; MAA, managed access agreement; MPS IVA, mucopolysaccharidosis type IVA; NWC: no wheelchair; PSM, propensity score matching; QW, weekly; SoC, standard of care; SWC: sometimes wheelchair; WCD: wheelchair dependent.

1.6 Summary of ERG's preferred assumptions and resulting ICER

Presently, the ERG cannot ascertain its preferred assumptions to be used in the economic model. Nonetheless, once the clinical data have been re-analysed and shared with the ERG, further conclusions are likely to arise. In Section 6.2, the ERG provided a list of recommended exploratory analysis to be undertaken by the company, while Section 6.1 includes the modelling errors identified by the ERG. The ERG also included a list of further clarifications to be provided by the company which can be found in Section 6.3.

2 Introduction and background

2.1 Introduction

This report provides a critique of the evidence submitted by BioMarin International Limited and BioMarin (U.K.) Limited to the Highly Specialised Technology (HST) evaluation programme in support of the clinical and cost effectiveness of elosulfase alfa (Vimizim®), hereafter referred to as ESA, as a regimen for treating mucopolysaccharidosis type IVA (MPS IVA, also known as Morquio A syndrome) in people of all ages.

2.2 Background

MPS IVA is a rare autosomal recessive genetic disorder and it is caused by the deficiency of the GALNS enzyme because of mutations in the GALNS gene.[1] Elosulfase alfa is an enzyme replacement therapy which aims to replace the deficient GALNS enzyme. The Evidence Review Group (ERG) notes MPS IVA is a heterogenous condition that can result in a wide spectrum of disease symptoms.[2, 3] For patients with more severe disease, MPS IVA typically reduces life expectancy and the cause of death is commonly due to respiratory complications.[4]

Within Sections A and B of the company submission (CS), the company provides an overview of:

- MPS IVA, including the associated morbidity and mortality, its impact on quality of life and current disease management (CS, Section B 6-8); and
- ESA, including its mode of action, dose and method of administration (CS, Section A 2).

Based on advice from its clinical experts, the ERG considers the CS to present an accurate overview of the morbidity and mortality associated with MPS IVA and the current treatment options. The ERG notes that ESA has been available to NHS patients in England via a managed access agreement (MAA) since the NICE highly specialised technologies guidance 2 of ESA (HST2) was published in 2015.[5] This review comprises a re-evaluation of HST2, in line with the completion of the MAA. The ERG considers key clinical data on ESA for this re-evaluation to be the data that was collected as part of the MAA, and notes that the company has also supplied supplementary data from a large number of clinical studies of ESA, most of which are non-comparative or observational studies. The ERG notes that most of the clinical trials (MOR-100, MOR-005, MOR-006, MOR-007 and MOR-008) were ongoing in 2015 at the time of HST2 and the company reports that their clinical trial programme for ESA has now completed. However, there is still an ongoing observational study, the Morquio A

Registry Study (MARS), which has enrolled both patients from the completed ESA clinical trials and newly treated patients and is due to complete in 2025.

The ERG notes that ESA is positioned by the company for treatment of MPS IVA as soon as possible after the diagnosis has been established. The ERG and its clinical experts agree with the company's proposed positioning of ESA and agree that the only relevant comparator is standard of care (SoC). SoC comprises a variety of different supportive or palliative care treatments, which includes medications and surgical procedures to relieve symptoms and address the complications of MPS IVA.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE, together with their rationale for any deviation from the final scope (Table 13). The company highlights that the submission differs from the final scope primarily in terms of the outcomes of interest to the decision problem. The key differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow.

Table 13. Summary of decision problem (Adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	People with mucopolysaccharidosis type IVA	No change	n/a	The ERG's clinical experts reported that now clinical practice with ESA is established due to the MAA, there will be fewer adult patients initiating treatment with ESA. In clinical practice, treatment is now more likely to commence in childhood nearer to the time of diagnosis. Nevertheless, the ERG notes that treatment will continue into adulthood and the ERG's clinical experts reported that the baseline characteristics of patients in the MAA are generally representative of the patients in England on ESA. The ERG also notes that MPS IVA is a heterogenous condition and that the patient populations in the various ESA trials vary considerably due to the different inclusion and exclusion criteria. These differences are reflected in the baseline characteristics of the studies and the ERG is thus concerned that the company's approach to use naïve comparisons potentially makes the comparison of ESA to SoC unreliable. In addition, the ERG is concerned that a consistent cohort of patients is not used at each timepoint in the current analyses of multiple different timepoints from baseline. This is discussed further in Section 3.2. The company has also presented the results of a PSM for 6MWT in their clarification response, which the ERG notes is sensitive to the PSM method used. Please see Sections 2.3.1 and 3.5 below for further detail.

Intervention	Elosulfase alfa (Vimizim®)	No change	n/a	The ERG notes that the dose of elosulfase alfa (ESA) in some of the MOR clinical trials was not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW). In particular, in MOR-002 all patients took part in dose escalation (ESA 0.1 mg/kg/QW for weeks 1–12, 1.0 mg/kg/QW for weeks 13–24 and 2.0 mg/kg/QW for weeks 25–36 and then could enter an extension period of 1.0 mg/kg/QW before MOR-100 where the dose was 2.0 mg/kg/QW), and in MOR-004 there were two active treatment groups, with one comprising alternate week dosing rather than weekly ESA. In addition, MOR-005, which was the extension study for MOR-004, comprised a re-randomisation of placebo patients from MOR-004 to the weekly or alternate weekly ESA dose along with continuation of treatment on either weekly or alternate weekly ESA. The ERG is concerned that these differences in ESA doses may confound the efficacy results, in particular for the Ex-Trial patients in the MAA as it includes patients from both MOR-005 and MOR-002.The ERG considers the 2.0 mg/kg/QW-QW subgroup results for MOR-005 are more reliable than the overall study results and the enzyme replacement therapy (ERT)-Naïve subgroup from the MAA are more reliable than the Ex-Trial subgroup. Please see Sections 2.3.2 and 3.2 below for further details.
Comparator(s)	Established clinical management without elosulfase alfa	No change	n/a	There are limited head-to-head trial data for ESA versus placebo from the RCT MOR-004, which comprised only 24 weeks' follow-up and the company reports that the placebo arm reflects an 'enhanced' SoC. The majority of the comparator data presented in the CS comprises naïve comparisons using data for SoC from

				MOR-001, a natural history study. The ERG considers that limited information is provided on the treatments received by patients in MOR-001, although the ERG's clinical experts also reported that there is no standard treatment in clinical practice and treatments would be individualised to manage the symptoms of each patient. MOR-001 is discussed further in Sections 2.3.3 and 3.2.2. Additionally, the ERG has concerns with the PSM analyses conducted by the company during the clarification stage and the ERG [redacted] The PSM analyses are discussed further in Section 3.5.
Outcomes	The outcome measures to be considered include: •endurance; •mobility; •respiratory and cardiac function; •growth and development; •vision and hearing; •sleep apnoea; •fatigue; •pain; •mortality; •adverse effects of treatment;	Clinical outcomes: •uKS; •6MWT; •Lung function (FVC, FEV1); •Ejection fraction; •Antibody titres. Quality of life/Activities of daily living: •MPS HAQ – Caregiver domain; •EQ-5D; •Adolescent and pediatric pain tool/Brief Pain Inventory;	Specific outcomes agreed and measured as part of the MAA. The systematic review also captures outcomes broader than those measured in the MAA.	The ERG notes that some of the outcomes listed in the NICE final scope are not explicitly covered in the CS (e.g. fatigue, sleep apnoea, and vision and hearing), although the ERG acknowledges that some of these are potentially incorporated within the quality of life measures. In addition, the ERG notes that growth and development data from the MAA were limited to change in weight. The ERG is concerned about the focus of wheelchair status in the economic model but notes that clinical effectiveness data on 6MWT and lung function outcomes are also provided in the CS. The ERG's clinical experts considered the outcomes collected in the MAA study to be of clinical relevance and the ERG considers 6MWT and lung function outcomes to be important outcomes for the assessment of response to treatment with ESA.

	•health-related quality of life (for patients and carers). Other outcomes collected in the managed access agreement: •neutralising antibodies; •urinary keratan sulfate;	•Beck Depression Index.		
Nature of the condition	•disease morbidity and patient clinical disability with current standard of care; •impact of the disease on carer's quality of life; •extent and nature of current treatment options.	No change	n/a	–
Clinical effectiveness	•overall magnitude of health benefits to patients and, when relevant, carers; •heterogeneity of health benefits within the population; •robustness of the current evidence and the contribution the guidance might make to strengthen it;	-	-	-

	•treatment continuation rules.			
Value for money	•Cost effectiveness using incremental cost per quality-adjusted life years gained; •Commercial agreements; •The nature and extent of the resources needed to enable the new technology to be used;	Updated with current standard costs.	n/a	-
Impact of the technology beyond direct health benefits	•whether there are significant benefits other than health; •whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services; •the potential for long-term benefits to the NHS of research and innovation; •the impact of the technology on the overall delivery of the specialised service;	Updated with information from the MPS Society.	n/a	The company's base case includes costs and QALY decrements for carers of patients. Carers costs are the key driver of SoC costs in the model, amounting to [redacted]% of total costs for the comparator arm.

	•staffing and infrastructure requirements, including training and planning for expertise.			
Special considerations, including issues related to equity or equality	•Guidance will only be issued in accordance with the marketing authorisation. •Guidance will take into account evidence considered in the evaluation of elosulfase alfa (HST2) and any further evidence that has become available since, including evidence collected in the elosulfase alfa managed access agreement. •If evidence allows, subgroup analysis by genotype and age will be considered.	–	–	The ERG considers the value of subgroup analyses is potentially limited due to the non-randomised and non-comparative nature of most of the studies on ESA and SoC. Nevertheless, the ERG notes that for some of the outcomes in the MAA, data is reported for subgroups by age (See Section 3.3 for results). The ERG does not consider subgroups by genotype to be covered within the CS. However, the ERG's clinical experts reported that genotype is not currently used as a marker of prognosis in MPS IVA as the condition is heterogeneous and it is not possible to accurately predict from all the potential mutations, which clinical symptoms will manifest.

Abbreviations: 6MWT, 6-minute walk test; CS, company submission; ERG, Evidence Review Group; ESA, elosulfase alfa; FEV1, Forced expiratory volume in 1 second; FVC, forced vital capacity; MAA, managed access agreement; MPS IVA, mucopolysaccharidosis type IVA; n/a, not applicable; PSM, propensity score matching; QW, weekly; SoC, standard of care; uKS, Urinary keratan sulfate.

2.3.1 Population

The ERG notes that patients with MPS IVA comprise a heterogenous population and that the clinical studies of ESA submitted by the company each differ in terms of their inclusion and exclusion criteria. For example, MOR-004 was a placebo controlled randomised control trial (RCT) that included patients above the age of 5 years and with an ability to walk between 30 m and 325 m in 6 minutes, which the company reported was stipulated to ensure maximum sensitivity to the primary end-point. MOR-004 was limited to a duration of 24 weeks and excluded participants who had major surgery within 3 months prior to study entry or planned major surgery during the 24-week treatment period. Patients from MOR-004 were eligible for a longer term follow-up study, MOR-005, in which patients were allowed to undergo surgery and so surgery is a potential confounder given it was not permitted in MOR-004 which comprised the first 24 weeks of ESA treatment for the patients in MOR-005.

MOR-002 was a dose-escalation study in MPS IVA patients aged 5 to 18 years and did not pre-specify a baseline 6-minute walk test (6MWT) threshold. However, MOR-006 included patients aged 5 years and above with limited mobility, which was defined as unable to walk >30 m in a 6MWT. Mobility in MOR-006 was thus lower at baseline compared to MOR-004 and MOR-002 excluded patients aged over 18 years, whereas MOR-004, MOR-005 and MOR-006 included patients over 18 years of age. MOR-007 was conducted exclusively in patients <5 years of age, whereas MOR-002, MOR-004, MOR-005, and MOR-006 were all in patients aged 5 years and above. MOR-008 included patients aged at least 7 years and who could walk at least 200 m in the 6MWT.

The MAA had detailed exclusion and starting criteria that did not comprise any restrictions based on age or baseline 6MWT (Table 14). The ERG's clinical experts reported that clinical heterogeneity is a known feature of MPS IVA and that they considered the patients in the MAA to be representative of typical patients who would be eligible for ESA in the UK.

Table 14. Exclusion and starting criteria of the MAA (Reproduced from CS, Table 8)

Elosulfase alfa will not be started if any of the following apply:
•The patient is diagnosed with an additional progressive life limiting condition where treatment would not ovide long-term benefit (e.g. cancer or multiple sclerosis); or
•The patient has a lung capacity (forced vital capacity) of <0.3 L and requires ventilator assistance; or

•The patient is unwilling to comply with the associated monitoring criteria: •All patients are required to attend their clinics three times a year for assessment; •All patients will sign up to the 'Managed Access Patient Agreement'.[6]
All the following are required before treatment is started: •All patients must have a confirmed diagnosis of MPS IVA as per the diagnosis criteria recommended in •All patients must have confirmed enzymatic test, elevated urinary keratan sulfate and mutation alysis; •In addition, patients aged ≥5 years can only start once a full set of baseline assessments has been tained, and they have signed the Managed Access Patient Agreement.

The ERG notes that the MAA (N=[redacted]) comprises two subpopulations:

- Enzyme replacement therapy (ERT)-Naïve patients (n=[redacted]) – patients who start ESA upon entry to the MAA; and
- Ex-Trial patients (n=[redacted]) – patients who have originated from the MOR clinical trial programme.

The MAA Ex-Trial patients originated from:

- MOR-002 (n=[redacted]);
- MOR-004/005 (n=[redacted]);
- MOR-006 (n=[redacted]); and
- MOR-007 (n=[redacted]).

The ERG thus considers the Ex-Trial population of the MAA to comprise a more heterogeneous population than the ERT-Naïve population, given the differences in inclusion and exclusion criteria for the clinical trials from which the Ex-Trial patients originated. In addition, the ERG notes that there are [redacted] (please see Section 3.2.5 and 3.3 for further details). As discussed in Section 2.3, the Ex-Trial patients entering the MAA were required to meet the MAA inclusion criteria but the ERG considers these to be much broader than the inclusion criteria of the clinical trials. However, the MAA also had specific criteria that were

required to be met on an annual basis for ESA treatment to be continued and the ERG is not aware of any such criteria in the clinical trials.

The company also reported that there was a multicentre, multinational, observational registry study, MARS, that was collecting long-term safety and efficacy data for up to 10 years on patients with MPS IVA and is due to complete in 2025. The company reported that the only exclusion criterion for MARS was current participation in a clinical trial for ESA. It should also be noted that patients are not required to be on ESA to be included in the registry. MARS includes several sub-studies from which additional data are collected, for example, on patients who have completed the MOR-005 and MOR-007 clinical trials and agreed to participate in the registry, and on patients who become pregnant after receiving ESA. However, the only data from MARS reported in the CS were limited to those from two conference posters on the patients who had been treated with ESA: one on efficacy outcomes at 5 years and the other on safety. The ERG notes that the 5-year MARS data comprise data from 325 patients, of which 262 are ESA-treated patients (143 patients initiated ESA independent of clinical trials) and the remaining patients are not on ESA. Despite the large number of patients in MARS, the ERG considers the MAA of more relevance to the NICE decision problem as the MAA exclusively comprises patients from England and Wales. The ERG also notes that no data on wheelchair use, the key clinical input for ESA in the company's economic model for this appraisal, are reported in the publications for MARS and the ERG is unsure whether data on wheelchair use have been collected.

2.3.2 Intervention

The ERG notes that European marketing authorisation for ESA was granted in 2014, although the ERG notes that a condition of the authorisation was that the company was required to set up a MPS IVA disease registry to assess the long term safety and efficacy of elosulfase alfa with submission of the final study report due in March 2025.[8] The disease registry is known as MARS and is discussed above in Section 2.3.1.

As discussed previously, ESA is available to patients with MPS IVA in England, via the MAA. The recommended dose of ESA is 2 mg/kg of body weight administered once a week as an intravenous (IV) infusion. The company report that treatment is expected to be lifelong, "*subject to clinical judgement and/or the application of any protocols or criteria that would lead to a decision to discontinue treatment*." The company also reported that, "*following specialist initiation and stabilisation of the patient on ESA, the infusion is then delivered in a homecare*

setting by a trained nurse". The ERG's clinical experts agreed with this, although they also reported that a small minority of patients might still attend hospital for some or all of their IV infusions.

The ERG notes that the Ex-Trial patients in the MAA may have originally commenced treatment on different doses or frequencies of ESA to that specified in the EU marketing authorisation and MAA treatment specification. The impact of this on the outcomes seen in the MAA is unclear. By contrast, the enzyme replacement therapy (ERT)-Naïve patients in the MAA will have received the recommended dose of ESA from the start of their treatment but there is less follow-up data available for this cohort as it is constrained by the duration of the MAA. The ERG considers that both the longer term follow-up data from the Ex-Trial MAA patients and the data from the ERT-Naïve patients are of value in assessing the clinical efficacy of ESA.

Patients from MOR-004 were eligible to enter the MOR-005 extension study, but this involved re-randomisation of the placebo patients from MOR-004 as they were also randomised to active ESA treatments in MOR-005. The ERG is concerned about the impact of the delay to treatment for the ex-placebo patients in MOR-005 on the results for ESA and how this might compare with ESA use in routine clinical practice. As such, the ERG considers the most robust source of evidence to be from the 2.0 mg/kg/weekly (QW) trial arm of MOR-004 and then the same patient population who continued through MOR-005 (where they would be considered a subgroup of patients that received ESA 2.0 mg/kg/QW in MOR-005 [ESA 2.0 mg/kg/QW-QW]).

The MAA has strict criteria that are assessed to confirm a patients' eligibility for treatment continuation with ESA and the ERG notes that these vary depending on whether the patients were ERT-Naïve or Ex-Trial (Table 15). The ERG notes that the thresholds for improvement in walking test and lung function from baseline differ slightly between the ERT-Naïve and Ex-Trial patients and is unsure of the rationale for the differences. However, the ERG also notes that [redacted] from the MAA was reported to discontinue treatment due to failure to meet the treatment criteria.

Table 15. MAA criteria for maintaining treatment (Reproduced from CS, Table 9)

Clinical criteria (for ERT-Naïve patients)
•Improvement in 6MWT distance or the timed 25-foot (7.6 m) walk (T25FW) of ≥10% over baseline or stabilisation after 10% improvement;
•Improvement in FVC or FEV1 of ≥5% over baseline or stabilisation after 1 year;

•Decline in LVEF of <10% from baseline; •Decline of uKS of ≥20% from baseline (and stabilised).
Ex-Trial patients •6MWT or T25FW remains ≥5% above the baseline value at the start of treatment; •FVC and FEV1 remain ≥2% above the baseline value at the start of treatment; •uKS levels remain reduced ≥20% from baseline; •Decline in LVEF of <10% from baseline.
PRO criteria (for ERT-Naïve patients and Ex-Trial patients) No adverse change in numerical value of two out of three of the following: •EQ-5D-5L score OR MPS-HAQ Caregiver Burden score; •Beck Depression Score (≥13 years); •APPT/BPI pain severity score (depending on age).
Abbreviations: 6MWT, 6-minute walk test; APPT, Adolescent Pediatric Pain Tool; BPI, Brief Pain Inventory; EQ-5D-5L, EuroQol 5 dimensions, 5 levels; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MPS-HAQ, MPS Health Assessment Questionnaire; PRO, patient-reported outcome; uKS, urinary keratan sulfate.

2.3.3 Comparators

The ERG notes that the comparator specified in the NICE final scope is established clinical management without ESA (referred to hereafter as SoC) and the ERG's clinical experts reported that there is no single specific comparator as treatment will be dependent on an individual patient's symptoms and disease severity. The company reports that the most relevant study to inform SoC is their own natural history study, MOR-001. However, the ERG is concerned about the lack of detail on the methods used by the company to identify MOR-001. The alternative SoC data presented in the CS is from the placebo arm of the 24 week MOR-004 RCT. The company reports that placebo in MOR-004 represents 'enhanced care' although no further details are provided. The ERG is concerned that the MOR-004 data are limited to 24 weeks, whereas MOR-001 has data for at least 2 years.

MOR-001 started in 2008 as a cross-sectional study of patients with MPS IVA with no restrictions on age or symptom severity but was changed to a longitudinal study in 2011. People with a previous haematopoietic stem cell transplant (HSCT) or with a concurrent medical condition that would likely interfere with study participation or pose a safety concern were excluded from MOR-001. In addition, if patients entered a clinical trial of ESA, they were excluded from further assessments in MOR-001. No details on the symptomatic treatments received by patients in

MOR-001 was provided in the CS, other than a breakdown of number and type of surgical procedures received by patients. However, the ERG notes that equivalent data on additional treatments for symptom control in patients in the MAA and MOR-005 were not reported in the CS.

MOR-001 included more than 353 patients and the company used the full trial population in naïve comparisons with the ESA data from the MAA. In addition, the company used data that appear to be from *post hoc* subgroup analyses of MOR-001, that were designed for matching SoC patients from MOR-001 with ESA patients from MOR-005, to enable naïve comparisons of ESA with SoC for the intention to treat (ITT) population and modified per protocol (MPP) population of MOR-005. Further details of the matching are discussed in Section 3.2.2.

In addition to the naïve comparisons between ESA and MOR-001, the company provided a propensity score matching (PSM) analysis for

[redacted]

The ERG provides further critique of the PSM analyses in Section 3.5.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a clinical systematic literature review (SLR), and provided the SLR protocol and search strategies in the appendices to the company submission (CS). The Evidence Review Group (ERG) considers the company's research question to be lacking in covering the comparator (established clinical management without elosulfase alfa treatment, hereafter referred to as standard of care [SoC]): "What randomised, non-randomised or single arm studies/case series have been conducted with elosulfase alfa in Morquio A, published or as yet unpublished?". The ERG is, therefore, unclear as to how the company identified and selected MOR-001 as the best source of data for SoC as there is no evidence of a SLR to identify other potential studies of relevance for the clinical effectiveness review.

The searches for the clinical SLR for studies of ESA were conducted in October/November 2019 and updated in November 2020. The electronic database searches from October 2019 identified 650 citations and after first pass (title/abstract) screening, 68 papers were screened at second pass (full text). Following full paper review, 17 articles were included from electronic sources,[2, 9-24] and a further 19 citations from the hand-searching.[9, 25-44] A total of 36 citations were, therefore, included in the original SLR and a further 8 new citations[45-53] were identified in the November 2020 update search. The ERG notes that in total 44 citations were included but the ERG is unclear as to the exact number of studies included as within the 44 citations there are multiple publications for some studies. The company provided tables in the CS summarising the included citations and the corresponding study name, although they were split across three tables (CS tables 13 to 15) and for some studies there were duplicate entries in the same table albeit for different citations. The ERG therefore found the results of the company's clinical SLR lacked clarity but notes there are over 20 included studies.

The ERG also considers the company's handling of the included studies following their inclusion in the SLR to lack clarity and considers it to be uncertain whether all available results are reported in the CS. The ERG notes that not all studies had quality assessments conducted and again the rationale for this is unclear. The ERG also considers it important to highlight that the company excluded the citation for MOR-008 (Burton *et al.* 2015[54]) from the SLR because MOR-008 was a pilot study. However, the company still presented the results of MOR-008 in the CS and the ERG

considers it to have data of potential relevance and so would disagree with its exclusion from the SLR (a summary of the methods of MOR-008 is provided in Appendix 8.2).

Of the included studies in the company's SLR, the ERG considers the weekly (QW) subgroup of MOR-004, the QW-QW subgroup of MOR-005, and the MAA to be of the most relevance to the NICE final scope. This is because the MAA reflects treatment with ESA of UK patients since the NICE appraisal of ESA in HST2 and the QW, and QW-QW subgroups of MOR-004 and MOR-005, respectively, comprise patients who have received the recommended EU licensed dose of ESA from the start of treatment and has collected outcome data on 6-minute walk test (6MWT) and lung function, which the ERG's clinical experts reported were key clinical outcomes of relevance. MOR-004 was a phase 3 study of ESA and MOR-005 is an extension study of MOR-004. These three key studies, along with the MOR-001 natural history study, are discussed further in Section 3.2.

Table 16. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	ClinicalSR report, Appendix 1, Subsection 1.	**The ERG considers the sources and dates searched appropriate.** Databases searched: Embase, Medline, Medline in Process/e-publications ahead of print (via PubMed), the Cochrane Library (CENTRAL, CDSR) and Database of Abstracts of Reviews of Effects (DARE) (Centre for Reviews and Dissemination, University of York [CRD]). Additional sources: Last two years of Society for the Study of Inborn Errors of Metabolism (SSIEM) conferences and of the WORLD Symposium (2018/2019), systematic review and meta-analysis reference lists, included trials reference lists, supplemental Google searches to identify full texts of abstracts identified in electronic searching, e-alerts from the PubMed search tracked until 13 November 2019 and cross-referencing from the economic and utilities SLRs. Latest search update: November 2020
Literature searches	ClinicalSR report, Appendix 1, Subsection 4.	**The ERG is satisfied that searches have identified all evidence on elosulfase alfa relevant to the decision problem but is**

		concerned sources were not searched appropriately to identify data for SoC. Search strategies combined comprehensive terms for the population (MPS IVA) and study design filters. Terms for elosulfase alfa (ESA) and comparators were not included in the search strategies. The ERG considers the company's approach to be appropriate despite some of the search strings used for study design being bespoke. However, the ERG is concerned that the searches did not seek to identify data on SoC.
Inclusion criteria	CS, Table 10.	**The ERG is concerned about the lack of a clinical SLR to identify data on SoC but considers it likely that no relevant evidence for ESA was excluded for the key outcomes of relevance for the economic model based on the eligibility criteria used.** The ERG notes that studies reporting only growth and/or height outcomes were excluded from the SLR, although growth was an outcome specified in the NICE final scope. The company's explanatory notes for exclusion state: "*Growth and height decreases (due to kyphosis or knee valgus*)", however, the ERG is unclear why the company has chosen not to include data on growth. Inclusion and exclusion criteria resulted in the inclusion of a large number of observational studies. The ERG considers it unclear as to the company's exact rationale for focusing on selected studies (MOR clinical trials, the MAA and MARS studies) in the clinical effectiveness section, although the ERG agrees that these are likely to be the most appropriate studies. Lists of studies excluded at full-text appraisal, together with reasons for exclusion, are provided. The ERG disagrees with the rationale for exclusion of one study (MOR-008),[54] which was attributed to it being pilot study but as the study was still reported and results presented in the CS the ERG is not concerned. No restrictions on language were applied.
Screening and data extraction	ClinicalSR report, Appendix 1, Subsection 6.	**The ERG notes that the initial abstract screening was conducted by a single senior reviewer and the ERG would prefer for this to have been done in duplicate as it is a vital**

		stage in the identification of literature. The ERG notes that the full text review was done in duplicate and the ERG considers the methods of data extraction were reasonable. A senior reviewer reviewed the abstracts and included any borderline eligibility articles for full text review. The full papers were reviewed by two reviewers independently in a blinded fashion with a third reviewer consulted when consensus could not be reached. Data extraction was quality checked by a second reviewer. The screening results for the original review were summarised in a PRISMA diagram and the updated review results were reported narratively.
Tool for quality assessment of included study or studies	ClinicalSR report, Section C, Subsection 3.1.5.	**The ERG considers the quality assessment tools used by the company for assessing the included RCT and observational studies were appropriate. However, assessment was not done for a large proportion of the included observational studies or the MAA.** As the observational studies were single-arm studies, the company used the Institute of Health Economics (IHE) QA checklist for case-series.[55] The ERG is unclear if quality assessment was done by one or two reviewers and, if so, whether the assessments were done independently. Detailed reasons were presented in support of the judgement of level of bias for each aspect of trial design covered in the assessment tool. The ERG notes that quality assessments were only conducted for the following studies: MOR-002/100, MOR-004, MOR-005, MOR-006, MOR-007. Quality assessments were not provided by the company for the MAA, MOR-001 or other included observational studies. In addition, due to time constraints the ERG was unable to undertake any quality assessments.

Abbreviations: CS, company submission; ERG, Evidence Review Group; ESA, elosulfase alfa; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; MAA, managed access agreement; MPS IVA, Mucopolysaccharidosis type IVA; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SoC, standard of care; SLT, systematic literature review.

3.2 Critique of trials of the technology of interest, the company's analysis, and interpretation

The key clinical studies from the company's clinical trial programme for ESA, along with the MAA study, the ongoing Morquio A Registry Study (MARS; clinicaltrials.gov NCT02294877) and the main study used by the company to inform SoC are summarised in Table 17.

The ERG notes that MOR-002, MOR-004, MOR-005, MOR-006, MOR-007 and MOR-100 are all reported to be either completed or terminated, whereas at the time of the original CS for HST2, only MOR-002 and MOR-004 were reported to be completed. It should also be noted that both MOR-002 and MOR-004 had associated extension studies:

- patients in the Phase 1/2 MOR-002 study could continue into MOR-100; and
- patients in the Phase 3 RCT MOR-004 could continue in MOR-005.

In addition, the data collection from the MAA has now been completed but MARS is ongoing and not due to complete until 2025.

As discussed previously, the ERG considers the MAA and the QW-QW subgroup from MOR-005 to be of the most relevance to the NICE final scope and from here on the ERG focuses its critique on these two studies for the effectiveness of ESA. In addition, MOR-001 is discussed and used to inform the comparator, SoC.

Table 17. Description of clinical studies (Adapted from CS, Table's 4 and 5)

Author and year of publication	Purpose of study (level of evidence) [ITT/PP]	Patients Number/Characteristics		Intervention and control	Follow-up period	Important endpoints (as reported by the company)
MOR-002[56]	Phase 1/2, open-label, dose-response study	n=20 (note: only weeks 25–36 at ESA dose 2.0 mg/kg/QW)	5–18 years	ESA: •0.1 mg/kg/QW (weeks 1–12); •1.0 mg/kg/QW (weeks 13–24); •2.0 mg/kg/QW (weeks 25–36)	48 weeks	6MWT, 3MSCT, FVC, MVV, uKS and side effects
MOR-100[57]	Open-label extension study for patients from MOR-002	n=18	5–18 years	ESA 2.0 mg/kg/QW	72 weeks	6MWT, 3MSCT, FVC, MVV, uKS, side effects and biochemical markers of bone and cartilage metabolism
MOR-004[58]	Phase 3, randomised, double-blind, placebo-controlled study in patients with a 6MWT distance between 30 m and 325 m	n=176 (n=58 for ESA dose 2.0 mg/kg/QW)	≥5 years	ESA 2.0 mg/kg/QW or QOW Placebo	24 weeks	6MWT, 3MSCT, uKS concentration
MOR-005[12, 13]	Two part open-label extension study for	n=173	≥5 years	ESA 2.0 mg/kg/QW or QOW	Up to 240 weeks but data limited to 120 weeks in CS	Side effects (number and seriousness), 6MWT, 3MSCT, uKS concentration, and

	patients from MOR-004	(n=56 for ESA dose 2.0 mg/kg/QW from start of MOR-004)				biochemical markers of bone and cartilage metabolism
MOR-006[10]	Phase 2, open-label study in patients with limited mobility (unable to walk >30 m in 6MWT)	n=13	≥5 years	ESA 2.0 mg/kg/QW	48 weeks	FDT, GPT, 25FWT, BPI-short, APPT, PODCI, SF-36, lung function, sleep apnoea, KS concentration, cardiac function, growth, bone density, spinal cord morphology, pain medication, endurance, exercise capacity, and biochemical markers of bone and cartilage metabolism
MOR-007[31]	Phase 2, open-label study in young patients <5 years	n=15	<5 years	ESA 2.0 mg/kg/QW	52 weeks	uKS, growth, side effects
MOR-008[54]	Phase 2, double-blind, pilot study of two doses of ESA	N=25 (N=15 on ESA 2.0 mg/kg/QW)	≥7 years	ESA 2.0 mg/kg/QW ESA 4.0 mg/kg/QW	27 weeks (followed by extension phase)	Safety, exercise capacity (cardiopulmonary exercise test [CPET]), lung

						function, pain, muscle strength
MOR-001 (MorCAP)[2, 57]	Natural History Study	N=353	1–65 years	Standard of care	104 weeks	6MWT, 3MSCT, FVC, MVV, uKS
Morquio A Registry Study (MARS)	Patient registry, includes sub-studies for MOR-004/005 and MOR-007	N=325	0–69 years	ESA and standard of care	10 years (currently in year 5)	Safety, 6MWT, FVC/FEV1, urine KS
Managed Access Agreement	Cohort study of English patients for conditional reimbursement	N=[redacted]	2–49 years	ESA 2.0 mg/kg/QW	Four years	uKS, 6MWT, FVC/FEV1, Ejection Fraction, QoL/ADLs

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; APPT, Adolescent Pediatric Pain Tool; CS, company submission; ESA, elosulfase alfa; FDT, functional dexterity test; FVC, forced vital capacity; GPT, grip and pinch test; ITT, intention to treat; MVV, maximal voluntary ventilation; PP, per protocol; QoL, quality of life; QOW, every other week; QW, weekly; uKS, urine keratan sulfate.

3.2.1 MOR-005

All patients in MOR-005 originated from the 24-week MOR-004[59] three-armed RCT (placebo, ESA 2.0 mg/kg/QoW with placebo infusions alternate weeks, and ESA 2.0 mg/kg/QW). Patients in MOR-004 were required to have mucopolysaccharidosis IVA (MPS IVA), be aged ≥5 years and have a 6MWT of between 30 m and 325 m, and both age and 6MWT were used as stratification factors.

Following completion of MOR-004, patients were eligible for entry into MOR-005, which comprised two parts and lasted for up to 240 weeks:

- Part 1 = continuation of randomised treatment with ESA and for placebo (PBO) patients, re-randomisation to either ESA 2.0 mg/kg/QoW or ESA 2.0 mg/kg/QW at the start of MOR-005. Treatment in Part 1 continued until the primary analysis of MOR-004 was complete (30/11/2012) and there were thus four ESA treatment groups in MOR-005: PBO-QOW, PBO-QW, QOW-QOW and QW-QW.
- Part 2 = initiated on 01/12/2012, an open-label study with all patients transitioned to receive the optimal treatment regimen of ESA as determined by MOR-004 (ESA 2.0 mg/kg/QW). The ERG notes that the specific time of transition to Part 2 for each patient was dependent on their date of study enrolment and ranged from Week 36 to Week 96[60] (the ERG notes that in the clinical study report [CSR] for MOR-005 the timing of Part 2 is reported to be from Week [redacted] and not Week 36).

As discussed previously, the ERG considers the results from the subgroup of patients in MOR-005 who have been on the recommended dose of ESA from the start of MOR-004 to represent the most relevant population for this appraisal, that is the ESA 2.0mg/kg/QW dose also referred to as the QW-QW subgroup from MOR-005. The ERG also notes that this is consistent with the company's view of the most relevant subgroup from MOR-005.

The ERG notes that the clinical data from MOR-005 at the time of HST2 were from an interim analysis at 72 weeks of ESA treatment, whereas the study has now completed and data for up to 264 weeks follow up are available. The data presented in the CS and publications of MOR-005 are limited to 120 weeks (from MOR-004 baseline or week 96 of MOR-005), which the company reported in their response to clarification questions (CQs) was because all patients had the

opportunity to complete at least 120 weeks of the study and beyond 120 weeks there was considerable drop-out. The company reported that the reason for the high dropout was mostly due to patients switching to commercial therapy and that no patient completed the planned 240 weeks of MOR-005.

The ERG notes that in the CS the company reports results from week 72 of MOR-005 to inform Year 1 from baseline despite the availability of some data at 48 weeks with no explanation for the rationale behind this decision. However, the ERG also notes from the Hendriksz *et al.* 2016c publication of MOR-005 that the Week 48 endurance assessments were performed only for subjects who reached Week 48 while in Part 1 of the study. That is, some patients moved to Part 2 prior to week 48 (as discussed above, the start of Part 2 was variable and occurred between Week 36 and Week 96). The ERG therefore agrees with the company that it is more appropriate to use the Week 72 data to inform one year although it would be beneficial to see a sensitivity analysis using the Week 48 data. The ERG agrees with the company's use of Week 120 data to inform Year 2 from baseline.

The ERG considers it important to highlight that the company did not report details of the number of patients remaining in MOR-005 beyond week 120 (from MOR-004 baseline) in the CS, although the company provided a CSR for MOR-005 which contained some detail on patient numbers at various subsequent timepoints. The ERG notes that in the clarification response the company reported that for the QW-QW subgroup of MOR-005 the mean duration of follow-up was 147.6 weeks (standard deviation [SD] 36.83) and the median was 141.3 weeks (range: 34.1 to 243.1 weeks). Following review of the data in the CSR, the ERG considers data from week [redacted] of MOR-005 are also of relevance to the decision problem and could be used to help inform the treatment effect of ESA at [redacted].

A further important characteristic of the data from MOR-005 is the analysis set. The company proposes the most relevant population is the modified per protocol (MPP) population, which comprises patients who maintained compliance of >80% and did not undergo surgery and is less restrictive than the per protocol (PP) population (49 patients excluded in MPP versus 95 patients excluded in PP). The company argue that the ITT population (all subjects who were enrolled into MOR-004 and continued into MOR-005, and who received at least one dose of ESA) is confounded by surgery and the subsequent period of recovery and that these directly impact the primary endpoint (6MWT) of the trial. The ERG notes that during MOR-004, elective surgery was

prohibited but surgery was allowed in MOR-005 as it was deemed unethical to continue to restrict access to surgery beyond the 24 weeks of MOR-004. The ERG considers the ITT population to be preferable to the MPP population. The ERG's rationale for preferring the ITT population is discussed further below.

A total of 38 patients were excluded from the full MOR-005 trial MPP population for undergoing orthopaedic surgery and from the data presented in the CS the ERG notes that the use of the MPP population (N=43) for the QW-QW subgroup results in the omission of 13 patients compared to the ITT population (N=56). The ERG agrees with the company that endurance test results can be impacted by the occurrence of orthopaedic surgery and the subsequent recovery period. However, based on clinical expert opinion, the ERG considers surgery is an integral part of the treatment pathway for patients with MPS IVA. The ERG therefore disagrees with the use of the MPP population for MOR-005 and instead considers the ITT population to be more representative of the expected treatment pathway for patients with MPS IVA. The ERG notes that its preference for the ITT population from MOR-005 is in keeping with the preferred population by the ERG of the previous appraisal of ESA (HST2).

The ERG notes that in the CS the company reports that the PBO arm of MOR-004 comprises 'enhanced care', although exactly what is meant by this statement is not reported. The ERG also notes that there are only 24 weeks of placebo data from MOR-004 and that all patients in MOR-005 received ESA, therefore there are no further comparative data for ESA versus SoC beyond 24 weeks. The ERG considers the 24 week placebo data from MOR-004 are of limited value, given the exclusion of patients undergoing surgery and the short follow-up in comparison to the 120 weeks available for ESA from MOR-005 and 2 years for SoC from MOR-001. The ERG's critique of the data available for SoC from MOR-001 is provided in Section 3.2.2.

Table 18 provides a summary of the methodology of MOR-004 and MOR-005 as reported in the CS, which the ERG notes is based on publications of the studies rather than the company's CSRs and the ERG is concerned that Table 18 is thus not fully representative of all characteristics of the studies. For example, the ERG notes from the CSR of MOR-005 that there is follow-up and outcome data for [redacted] and there are also data on [redacted] detailed in Table 18. The ERG also considers it important to highlight that the table relates to the full trial methodology, whereas the ERG considers the QW subgroup of MOR-004 and the resulting QW-QW subgroup of MOR-005 to be of most relevance. The ERG

discusses only the MOR-005 QW-QW data from here onwards and, although the ERG preference is for the ITT population, the ERG also discusses the MPP results for completeness. The ERG has not conducted an independent quality assessment of MOR-005 due to time constraints but considers the company quality assessment does not emphasise the open label nature of part 2 of MOR-005, which forms a large proportion of the data (Appendix 8.1). In addition, the ERG considers it unusual that the company has reported that the methods of randomisation and allocation concealment of their own study is unknown.

In terms of patient withdrawals, the ERG notes that only one patient from the ESA QW subgroup (N=58) withdrew from MOR-004 and this was due to withdrawal of consent by the patient. In addition, a further patient did not enrol in MOR-005. The resulting ITT QW-QW subgroup of MOR-005 therefore comprised 56 patients and one of these discontinued prior to Part 2 of MOR-005. Of the remaining 55 patients, two discontinued during Part 2 as a result of adverse effects and the remaining 53 patients remained until termination of the study. A Consort diagram was provided by the company for the ITT population in a clarification response, Figure 4. As discussed above, the MPP population comprised only 43 patients.

The ERG also considers it important to highlight that the ITT results for MOR-004 and MOR-005 presented in the CSR are based on the N=[redacted] population, whereas those presented for MOR-005 in the CS were for the N=[redacted] ITT. The ERG considers the N=[redacted] population to be the most appropriate number of patients. However, due to omissions in the data provided by the company the ERG has had to extract some data from the CSR and so for completeness the ERG presents the results for both where available. A further reason for the ERG's decision to report both sets of results is that the ERG is unsure what the company's definition of ITT is and how they have dealt with missing data in the analyses. The ERG is concerned that there are differences in the number of patients in the analyses beyond [redacted] weeks depending on which data source is used (CS or CSR) and given that enrolment for MOR-005 was following completion of MOR-004 Week 24, the number of patients in the analyses should only differ up to week 24. These differences are discussed further alongside the results in Section 3.3.

Table 18. Company's summary of the methodology of MOR-004 and MOR-005 (Reproduced from CS, Table 16)

Characteristic	MOR-004	MOR-005
Author, Year (main)	Hendriksz *et al.* 2014[58]	Hendriksz *et al.* 2016[60]
Design/population	Phase 3 double-blind RCT (PLA-controlled) in patients ≥5 yrs with 6MWT distance between 30 m and 325 m	Phase 3 extension, double blind then open label extension, patients ≥5 yrs
Intervention(s)	ESA 2.0 mg/kg QW ESA 2.0 mg/kg QOW	Double blind (part 1): ESA 2.0 mg/kg QW ESA 2.0 mg/kg QOW Open label extension (part 2): ESA 2.0 mg/kg QW
Comparator(s)	Placebo	N/A
Population	≥ 5 years, confirmed MPS IVA (documented reduced GALNS or genetic testing)	≥ 5 years, confirmed MPS IVA (documented reduced GALNS or genetic testing)
Objectives	To assess the efficacy and safety of enzyme replacement therapy with ESA in patients with MPS IVA	To present MPS-HAQ outcomes over 1 and 2 years in the MOR-004/005 trial and to compare these with MPS-HAQ outcomes over a similar time period in a comparable untreated cohort of MPS IVA from the MOR-001 natural history study

Location/Study setting	International, 17 countries (USA, ARG, BRA, CAN, COL, DNK, FRA, DEU, ITA, JPN, KOR, NLD, POR, QAT, SAU, TWN, UK)	International, 20 countries (USA, ARG, BRA, CAN, COL, DNK, FRA, DEU, ITA, JPN, KOR, NLD, NOR, POR, QAT, SAU, ESP, TWN, TUR, UK)
Study design	Phase 3, double blind RCT, parallel-arm	Phase 3 extension study: double blind RCT followed by open label extension
Duration of study	24 weeks	120 weeks
Sample size	Randomised 177 mITT=176 1 patient was randomised but not treated and was excluded because the diagnosis was not confirmed	Part 1: 173 Part 2: 169
Inclusion criteria	≥5 years with 6MWT distance between 30 m and 325 m, documented clinical diagnosis of MPS IVA	Completed MOR-004
Exclusion criteria	6MWT <30 m, 6MWT >325 m, HSCT or ESA-treated patients, surgery within 3 months of enrolment or planned in 24 weeks of study, symptomatic cervical spine instability, significant spinal cord compression, severe cardiac disease	Prior investigational product or device (other than ESA in MOR-004) within 30 days of baseline, previous ESA study other than MOR-004, concurrent disease that would interfere with participation or be a safety risk (e.g. symptomatic cervical spine instability, clinically significant spinal cord compression, severe cardiac disease)
Method of randomisation	Not reported but stratified by screening 6MWT category (≤200 and >200 m) and age group (5–11, 12–18, ≥19 years old)	Not reported, re-randomisation not stratified

Method of blinding	Described as double-blind. Statement "Patients, investigators and site personnel were blinded to treatment assignment throughout the study and until the final analysis was complete". Also, patients randomised to the arm with (active) treatment every other week were given placebo infusions on alternative weeks to mask active drug weeks	Described as double blind. Further, masking described as quadruple: participant, care provider, investigator, outcomes assessor
Treatment arms (NITT/ NmITT)	ESA 2 mg/kg/QW (58) ESA 2 mg/kg QOW (59) Placebo (59)	ESA 2 mg/kg/QW (56) ESA 2 mg/kg QOW (59) Placebo-QW (29) Placebo-QW (29)
Baseline differences	Treatment arms balanced at baseline	Randomisation on entry to MOR-005 was not stratified and a chance imbalance occurred in MOR-005 baseline characteristics (age and endurance measures)
How was follow-up conducted? Duration of follow-up, participants lost to follow-up	24 weeks, treatment compliance high, almost all patients completed study, after which they could enrol in MOR-005	120 weeks (including 24 weeks of MOR-004)
Statistical tests	ANCOVA model with baseline 6MWT category (≤200, >200 m) and age group (5-11, 12-19, ≥19 years) as covariates. For secondary endpoints, due to multiplicity, step-down testing procedure used (3MSCT had to show sig result first and only then could uKS be declared significant. Hochberg method for multiplicity adjustment used for the two treatment comparisons with placebo.	Descriptive stats. Repeated measures ANCOVA model (including treatment, time point, treatment and time point interaction, baseline age stratum (5-11, 12-18, ≥19 years), Baseline 6MWT distance stratum (≤200m, >200m), and baseline measurement (for 3MSCT and uKS) as factors) used to compare LS mean changes from baseline at Year 1 and Year 2 between MOR-005 and MOR-001 populations.

	Missing data was addressed using multiple imputation for primary, secondary and respiratory function endpoints (joint normal distribution)	Only patients continually on ESA 2.0mg/kg/QW were compared to MOR-001
Primary outcomes (including scoring methods and timings of assessments)	6MWT change from baseline at week 24 for each ESA group versus placebo	6MWT, 24 weeks, 36 weeks, 72 weeks, 120 weeks
Secondary outcomes (including scoring methods and timings of assessments)	3MSCT change from baseline at week 24 Norm uKS change from baseline at week 24	3MSCT, 24 weeks, 36 weeks, 72 weeks, 120 weeks uKS 120 weeks

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; ANCOVA, analysis of covariance; ARG, Argentina; BL, baseline; BRA, Brazil; CAN, Canada; COL, Columbia; DEU, Germany; DNK, Denmark; ESA, elosulfase alfa; FRA, France; GALNS, n-acetylgalactosamine-6-sulfate sulfatase; HSCT, haematopoietic stem cell transplant; m, metre; ITA, Italy; JPN, Japan; KOR, South Korea; mITT, modified intention to treat; NLD, The Netherlands; PLA, placebo; POR, Portugal; QAT, Qatar; QOW, every other week; QW, weekly; RCT, randomised controlled trial; SAU, Saudi Arabia; TWN, Taiwan; uKS, urinary keratan sulphate; UK, United Kingdom; USA, United States of America.

3.2.2 MOR-001

MOR-001 (also known as MorCAP) was a multicentre, multinational, observational study of patients with MPS IVA that commenced in 2008. MOR-001 was originally designed to be a single visit, cross sectional study of MPS IVA patients with no restrictions on inclusion related to age or MPS IVA symptom severity. However, MOR-001 was later amended to be a longitudinal study (date of amendment was reported as 2011).[2] In total, 353 patients were enrolled in MOR-001 and patients were required to discontinue from MOR-001 if they enrolled in an enzyme replacement therapy (ERT) clinical trial (i.e. a clinical trial of ESA); the ERG notes that 123 out of 353 patients discontinued for this reason.[57]

Data collected from MOR-001 comprise only 2 years of follow-up in the key publications cited in the CS and company clarification responses.[2, 57] In addition, the ERG notes that it is reported in the Harmatz *et al.* 2015 publication of MOR-001 that the amendment of the MOR-001 study design from cross-sectional to longitudinal resulted in the timing between baseline and year 1 varying between patients, as they were recruited to the original cross-sectional study at various calendar times. The ERG considers this to be a key limitation of the data and current analyses presented by the company using the MOR-001 data. The ERG notes that within the company's response to clarification, IPD data from MOR-001 were supplied to the ERG. Following review of these data the ERG noted that for some patients their Year 1 post-baseline assessment could have been [redacted] after their baseline assessment. From [redacted], and from the description in the Harmatz *et al.* 2013 publication, the ERG is concerned that the post-baseline assessment value is used to represent a patient's change from baseline at Year 1 irrespective of the true calendar time since baseline. This may over or under estimate the true natural history change from baseline for each outcome. In addition, if the patient had subsequent data collected beyond the Year 1 post-baseline assessment, the ERG is concerned that they also may not correctly correspond with the calendar time from baseline (e.g. the Year 2 assessment post-baseline may be informed by data actually collected 3 calendar years from baseline). While, the ERG considers it reasonable to round readings to the nearest year from baseline if data weren't collected at exactly the correct timepoint, to avoid losing a large amount of data (e.g. round 6 months or 17 months to 1 year), the ERG does not consider it appropriate to use readings from 2 years to inform the 1 year assessment or 3 years to inform the 2 year assessment.

The ERG notes from the IPD that there is potentially comparator data for SoC from MOR-001 at up to [redacted] years post-baseline, although the ERG is unsure of the patient numbers with data at each timepoint as the ERG has identified what appear to be multiple inconsistencies with the way the company has currently coded the data in the IPD file. However, the ERG is also concerned that the company's current analyses of the data from MOR-001 assume the same cohort of patients have been followed at each timepoint. For example, for MOR-001 there is a loss of over 50% of patients between Year 1 (n=184) and Year 2 (n=78) in the analyses of patients with data at baseline. Additionally, the ERG considers that it is unclear whether all patients in the Year 2 analysis are included in the Year 1 analysis.

The ERG considers a complete case analysis would be a more appropriate method of analysis of the data from MOR-001 given the high discontinuation rate and the known heterogeneity of MPS IVA. In addition, the ERG is concerned that the patients lost between Year 1 and Year 2 are unlikely to be missing at random because reasons for discontinuation from MOR-001 included commencing treatment with ESA. A complete case analysis would thus be beneficial to ensure a consistent cohort of patients are followed up in the SoC group as it is an analysis in which the same cohort of patients are included at baseline and each subsequent year for each individual outcome. The ERG acknowledges that such an analysis has limitations as we do not know the characteristics of the patients who are discarded from the analysis due to being 'incomplete' cases as the ERG considers it likely that patients are not missing at random. Nevertheless, given the heterogeneity in the disease presentation, the ERG considers it likely that baseline and subsequent assessments could be skewed by the extremely different outcomes of individual patients and thus it is important to have a consistent cohort of patients in order to draw any meaningful conclusions on changes over time with SoC.

The company did not provide a quality assessment for MOR-001 and due to time constraints, the ERG was unable to undertake one. The ERG considers the methods reported for MOR-001 are limited, which is partly a reflection of the main sources of detail on the study being from journal publications. However, the company did provide some additional details on the study in response to clarification questions.

The company reported that due to concerns regarding the short duration of the placebo arm in MOR-004, as well as the 'enhanced' care that they considered patients to have received, they consider MOR-001 to be the most relevant study to inform SoC. However, the company also

decided that the data from MOR-001 should be reanalysed to enable this comparison and they used two *post hoc* subgroup analyses of MOR-001:

- MorCAP1 = the subgroup of MOR-001 patients who were ≥5 years of age and had an average 6MWT distance ≥30 and ≤325 m at baseline as well as longitudinal data available at Year 1 and/or Year 2 follow-up. This subgroup was used by the company for the comparison of SoC with the ESA MOR-005 ITT population.
- MorCAP2 = this comprised further restricting the MorCAP1 subgroup to also exclude patients who underwent orthopaedic surgery within the 3 months prior to the time at which their baseline data were collected or during the 2-year MOR-001 follow-up period. This subgroup was used by the company for the comparison of SoC with the ESA MOR-005 MPP population.

As discussed previously, the ERG disagrees with the company's use of the MPP population from MOR-005. The ERG does, however, agree with the company's proposed use of the MorCAP1 subgroup of MOR-001 to inform the comparison of SoC with ESA in the ITT population of MOR-005. However, as discussed above, the ERG has serious concerns around the true comparability of the current MOR-001 data presented by the company due to the way in which it appears Year 1 has been arbitrarily defined based on it being the first assessment post-baseline rather than a true 1-year post-baseline assessment. In addition, it should be noted that the ERG also has concerns regarding the heterogeneity in the patient populations in the MOR-005 and MorCAP1 studies and differences in baseline characteristics (which are discussed further in Section 3.2.5). The ERG considers propensity score matching (PSM) adjusted analyses may have provided a more robust comparison between ESA and SoC but the ERG considers the handling of the MOR-001 data by the company needs to be clarified and if necessary, amended to ensure that the definition of 1-year post-baseline is consistent within and between all studies if any reliable comparisons between SoC and ESA are to be conducted.

3.2.3 Managed Access Agreement (MAA) in England

As previously discussed, the MAA has enabled [redacted] patients diagnosed with MPS IVA in England to have conditional access to treatment with ESA since December 2015. Clinical and patient-reported outcome data have been collected to support the review of the clinical effectiveness of ESA to the end of the MAA period, which was initially scheduled for December 2020, but has been extended by 12 months following agreement between NICE, NHSE, and BioMarin. The MAA

data collection has now been completed and no further patient outcome data will be collected for the 12-month extension period (ending in December 2021). The analyses presented in the CS are based on a data cut from the MAA from [redacted] and the ERG is unsure as to whether further data are available between [redacted].

The MAA comprised two groups of patients: enzyme replacement therapy Naïve (ERT-Naïve) patients who commenced ESA for the first time during the MAA (N=[redacted]), and Ex-Trial patients who had previously started ESA in one of the MOR clinical trials (N=[redacted]). The ERG notes that the Ex-Trial patients originated from MOR-002 (n=[redacted]), MOR-006 (n=[redacted]) and MOR-007 (n=[redacted]), in addition to MOR-005 (n=[redacted]). In fact, the ERG considers it important to highlight that each of these MOR clinical trials that fed patients into the MAA had differing inclusion and exclusion criteria, thus they comprise heterogenous populations. Please see below for a brief summary of the various MOR clinical trials from which the MAA Ex-Trial patients originated with more details of the studies provided in Appendix 8.2:

- **MOR-002:**[56] This was a completed phase 1/2 dose escalation study that comprised 20 MPS IVA patients. Patients were sequentially treated with three different doses of open-label ESA in increasing strengths starting at a dose of 0.1 mg/kg/week with the dose increased every 12 weeks and patients who completed the dose escalation could continue on a dose of 1.0mg/kg/week for 36 to 48 weeks. Patients therefore would only receive the recommended 2.0mg/kg/QW dose between weeks 25 and 36 of the study although treatment could be for up to 84 weeks. Patients could then transition to the extension study MOR-100 where treatment was ESA 2.0 mg/kg/QW for up to 192 weeks. The ERG considers it unclear whether the MAA Ex-Trial patients from MOR-002 included patients from MOR-100.
- **MOR-005:**[14] This was an open label extension study that followed on from MOR-004.[58] MOR-004 was a 24-week phase 3 multi-centre, randomised, double-blind, placebo-controlled study of ESA. MPS IVA patients aged between 5 and 57 years and able to walk between 30 and 325 m in MOR-004 were randomised to one of three arms: ESA 2.0 mg/kg/QW, ESA 2.0 mg/kg/QOW or placebo. Surgical interventions (e.g. orthopaedic surgeries) were not permitted during MOR-004 due to concerns they may be confounders, but the treatment period was limited to 24 weeks for ethical reasons to avoid extensive delay of necessary surgery. Patients who completed the MOR-004 study were eligible to enrol Into MOR-005 and if they were previously treated with placebo

then they were re-randomised to receive ESA 2.0 mg/kg/QOW or ESA 2.0 mg/kg/QW in the first part of MOR-005. All patients were subsequently transferred to ESA 2.0 mg/kg/QW in the second part of MOR-005 and were followed up for a minimum of 120 weeks treatment. Patients in MOR-005 were allowed access to surgery.

- **MOR-006:**[10] This was a phase 2 study of ESA 2.0 mg/kg/QW in 13 patients with impaired mobility, defined as a 6MWT ≤30 metres at baseline.
- **MOR-007:**[31] This was a phase 2 study of ESA 2.0 mg/kg/QW in 15 children aged under 5 years at baseline.

The ERG considers the Ex-Trial population of the MAA comprises a more heterogeneous population than the ERT-Naïve population given the differences in inclusion and exclusion criteria for the clinical trials from which the Ex-Trial patients originated. In addition, the ERG notes that there are notable differences across some of the baseline characteristics for the Ex-Trial patients compared to the ERT-Naïve patients and in turn there are marked differences in efficacy outcomes between the two MAA subgroups unrelated to duration of treatment with ESA. The baseline characteristics of patients in the MAA are discussed further in Section3.2.5, but the ERG considers it important to highlight that the ERT-Naïve subgroup has substantially less follow-up data compared to the Ex-Trial patients. Therefore, while the ERG acknowledges that the use of only the ERT-Naïve subgroup from the MAA restricts the available data, the ERG considers the ERT-Naïve subgroup from the MAA to comprise a less heterogenous patient population than the Ex-Trial subgroup. It also comprises a directly relevant MPS IVA patient population in which ESA would be used in clinical practice in England.

The eligibility criteria for patients to receive ESA treatment in the MAA are as discussed in Sections 2.3.1 and 2.3.2. Patients who enrolled in the MAA were monitored on an annual basis and had to fulfil the criteria detailed in Table 15 in order to continue ESA. The ERG's clinical experts reported that the MAA criteria were reasonable and were strictly adhered to in clinical practice.

Based on the [redacted] data cut, of the [redacted] patients enrolled in the MAA, [redacted] had stopped treatment with ESA during the study period, although where data were available, they were included in the analysis. The reasons for treatment discontinuation were voluntary in [redacted] patients ([redacted]). Two patients

enrolled in the MAA did not have any follow-up data suitable for inclusion in the analyses as they started within a year of the data cut and one patient had duplicated records, therefore, the data for analysis was from [redacted] patients (CS, Figure 11 provides a flow chart of the patients in the MAA). The ERG notes that [redacted] of the patients who discontinued treatment were from the Ex-Trial subgroup.

Statistical analyses for the MAA data included two-sample t-tests to compare the means of each population and subgroup analyses by age at treatment initiation (>18/≤18 years). Similar to MOR-001, the ERG is concerned that a consistent cohort of patients are not informing each timepoint in the outcome analyses for the MAA. As discussed previously, the ERG considers that given the known heterogeneity in MPS IVA disease presentation, it is likely that baseline and subsequent assessments could be skewed by the extremely different outcomes of individual patients. The ERG thus considers it important to have a consistent cohort of patients in order to draw any meaningful conclusions on changes over time with ESA. The ERG therefore considers a complete case analysis would be more appropriate.

In addition, the ERG considers there to be inconsistencies and flaws in the way the IPD from the MAA has been analysed. The ERG is particularly concerned that data may have been inappropriately included in analyses from [redacted] raising questions about the reliability of the data presented in the current analyses at fixed timepoints. For example, data for a patient who had data collected at [redacted]

The ERG notes that the company did not provide a quality assessment of the MAA in the CS and due to time constraints, the ERG was unable to conduct an assessment. Specific areas of concern to the ERG regarding the MAA and its data are nevertheless flagged where possible within this report.

3.2.3.1 MAA treatment duration

The company provided details of the ESA treatment duration for the ERT-Naïve and Ex-Trial patients in the MAA at the [redacted] data cut (Table 19). In addition, in response to a clarification question, the company also provided details of the Ex-Trial patients prior ESA

treatment duration at the MAA baseline. The ERG notes that treatment duration was calculated based on ESA treatment start date (irrespective of whether it was prior to the commencement of the MAA) and the last assessment available in the MAA data-cut. For the Ex-Trial patients, the treatment start date thus relates to ESA start in the original clinical trial. The ERG notes that mean ESA treatment duration for the Ex-Trial patients at baseline in the MAA was [redacted] and at the [redacted] data cut it was [redacted] with the maximum being [redacted]. ERT-Naïve patients had a mean treatment duration of ESA of [redacted] and a range of [redacted]. The MAA Ex-Trial population thus comprises [redacted] efficacy data for ESA than MOR-005 (maximum 264 weeks).

Table 19. Duration of treatment with elosulfase alfa for people participating in the MAA (Adapted from CQ response, Table's 23 and 24)

	Ex-Trial (patients initiate treatment before MAA)		ERT-Naïve (patients initiating treatment in MAA)
	Treatment duration at MAA enrolment, years	Treatment duration at last data point available in the MAA data cut, years	Treatment duration at last data point available in the MAA data cut, years
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: ERT, enzyme replacement therapy; MAA, managed access agreement; SD, standard deviation.

3.2.4 *Treatment adherence*

[redacted], although in MOR-005 17.4% of the infusions in the QW-QW subgroup were administered outside the 3-day dosing window.

3.2.5 *Baseline characteristics*

Comprehensive patient baseline characteristics for MOR-004, MOR-005, MAA, and MOR-001 were provided in the company response to clarification question A11. However, unfortunately, for MOR-001 baseline characteristics were only reported for the full trial population and MorCAP2, not MorCAP1 which is the ERG's preferred population for comparison with the MOR-005 QW-QW ITT population. The ERG also notes that the data for the MAA Ex-Trial patients shows only [redacted] patients have consistently received the 2.0 mg/kg/QW licensed dose of ESA from trial outset and [redacted] The ERG is unclear of the [redacted] but notes that, as discussed in Section 2.3.1, there is considerable heterogeneity across and within the studies which is likely partly related to the differing inclusion criteria for each of the studies as well as the heterogenous nature of MPS IVA.

There was a wide variation in the age range of patients included within the [redacted] The ERG's clinical experts reported that the wide age ranges reflected their expectations of the ages of patients with MPS IVA who would likely receive ESA.

The range of values for the baseline assessments of the outcome measures (e.g. 6MWT and FVC) within the studies were also wide, although for 6MWT in MOR-005 it was partly constrained by the MOR-004 study inclusion criteria. The ERG notes that many of the baseline values for the outcome measures were also highly variable between the studies, and [redacted] The exact baseline values are discussed alongside the change from baseline for each outcome in the respective subsection of the results Section 3.3. However, while the ERG considers the variation between the studies to be part of the heterogenous nature of MPS IVA, the ERG also considers it likely to impact on any naïve comparisons of results between the studies and that it is not possible to predict the likely direction of any resulting bias. The ERG therefore considers the naïve comparisons should be interpreted with caution and reiterates

that the ERG considers appropriate adjustment for any imbalances in baseline characteristics would be preferable, for example, PSM analyses.

3.2.6 Surgery

As discussed in Section 3.2.1, MOR-004 excluded patients who had major surgery within 3 months before study entry or planned major surgery during the 24-week study treatment period. However, patients in the extension study MOR-005 were allowed to undergo surgical procedures. The company provided details in their response to clarification questions of the number of patients who underwent surgery in MOR-005 and MOR-001, including a breakdown of the type of surgery received by patients.

A total of 24 surgical and medical procedures were performed in 14 (25.0%) of the patients in the MOR-005 QW-QW subgroup (N=56). No patient in the MOR-005 QW-QW population underwent spinal fusion or decompression surgery. The most frequent surgical and medical procedures in the MOR-005 QW-QW patients were medical device implantation (5.4% of patients) or removal (7.1% of patients), although no further details were provided on what these devices were.

The total incidence of surgical procedures for patients in MOR-001 was not provided but the incidence by type of surgery was provided and the ERG notes the incidence of procedures was generally higher in MOR-001 compared to in MOR-005. Ear tube insertion was the most common type of surgery in MOR-001, with an incidence of 25.2%. Spinal decompression occurred in 14.7% of patients and spinal fusion in 18.1% of patients.

The ERG notes that, like in MOR-001 and MOR-005, patients in the MAA were also allowed to receive surgical interventions, although data on the surgeries were not collected. The company reports that the absence of data on surgery is one of the limitations of the MAA, but the ERG considers it important to note that the MAA directly reflects clinical practice and the expected treatment pathway for MPS IVA patients who have received ESA in England. The ERG's clinical experts reported that patients on ESA would still be expected to have surgery for symptom control as deemed necessary, although the impact of ESA on the number and type of surgeries may differ compared to patients who were not on ESA. The ERG acknowledges that where surgical procedures have occurred in the studies, they may confound the efficacy results for SoC and ESA with the likely direction of bias impossible to predict. However, given that surgery is a

part of the expected treatment pathway, the ERG does not consider it appropriate to remove patients who have undergone surgery from the analyses. As discussed in Section 3.2.1, the ERG considers the full MOR-005 QW-QW population of more relevance to the decision problem than the MPP population. Likewise, the ERG considers MorCAP1 and the full MOR-001 populations of more relevance than MorCAP2, where patients undergoing surgery were excluded from the analysis.

3.3 Results

The ERG presents and discusses the results of the MAA, MOR-005 QW-QW and MOR-001 below. As discussed in Sections 3.2.1 to 3.2.3, the ERG is concerned with the company's current analyses of the data from MOR-001, MOR-005 QW-QW and the MAA. The ERG recommends extreme caution in drawing any conclusions based on the company's current analyses of the studies as the individual patients informing the various timepoints for each outcome vary and as such the population at baseline is not necessarily the same population at each timepoint. In addition, the ERG has identified potential serious flaws in the methods used to analyse the data such as [redacted] and the inclusion of data from inconsistent timepoints to inform outcomes at a timepoint. Finally, the ERG considers there to be inconsistencies between the data reported in the CS and [redacted]. As the ERG has fundamental concerns about the way the individual studies have been analysed it considers any subsequent analyses of the comparative effectiveness of ESA and SoC to be flawed.

The ERG considers it important to highlight that for most of the outcomes, the company reported the results for the MAA Ex-Trial and ERT-Naïve populations separately with no pooled analyses of the full MAA population. The ERG considers this approach reasonable given the heterogeneity in the patient populations that is evident from the baseline values. In addition, the company has presented change from baseline to end of follow-up data for the MAA patients and it should be noted that, while useful, the length of follow-up of patients in these analyses was highly variable. The ERG considers the change from baseline by year of follow-up to be of more relevance in terms of both assessing the efficacy of ESA and appropriateness for informing the economic model. However, the years of follow-up are limited by small patient numbers, a lack of data for some patients at all time points and potential flaws in the methods used to analyse the data as discussed in 3.2.3.

Also as discussed earlier, the ERG has included the MPP results alongside the ITT results for MOR-005 QW-QW, although the ERG considers the ITT results to be more appropriate. In terms of the MOR-001 data, the ERG considers the MorCAP1 data to be the best source of SoC data for comparison with ESA from the MOR-005 QW-QW ITT population, MorCAP2 as the best comparator for ESA in the MOR-005 QW-QW MPP population, and the full MOR-001 population for both of the MAA populations. Please see Section 3.2.2 for further details on the MOR-001 subgroups (MorCAP1 and MorCAP2).

The ERG has presented the results for ESA from the MAA and the MOR-005 QW-QW subgroup alongside the results for SoC from MOR-001 (including MorCAP1 and MorCAP2, where relevant) in the following subsections. However, it should be noted that aside from the ERG's concerns about the reliability of the actual data, the comparisons of ESA and SoC presented or discussed in the subsections of Section 3.3 below are mostly naïve comparisons. The ERG considers this important to highlight because the studies for ESA and SoC discussed below implicitly include all of the biases introduced by comparing non-randomised groups. Therefore, the ERG recommends caution in drawing any conclusions from the between study comparisons of ESA and SoC.

3.3.1 Endurance

3.3.1.1 6-minute walk test (6MWT) - MAA results

The company reported that at last follow-up for the patients in the MAA with available baseline and follow-up data (CS, Figure 19):

- [redacted]) had a mean (SD) baseline 6MWT distance of [redacted];
- [redacted]) had a mean (SD) baseline 6MWT distance of [redacted]).

The ERG notes that the mean baseline 6MWT distance was [redacted] in the Ex-Trial patients and the [redacted] compared to the ERT-Naïve patients [redacted]. In addition, the ERG notes that the data in Figure 1 suggest [redacted]

changes from baseline if the last year with follow-up data in Figure 1 is used rather than the data for mean value at last follow-up (reported above).

The ERG also notes that the SoC data from the full trial population of MOR-001 are included in Figure 1 and they suggest a [redacted] in 6MWT overtime. However, the SoC data are extrapolated beyond year 2 and despite being [redacted] at baseline to the MAA data, by two years 6MWT in MOR-001 is [redacted] thus suggesting ESA is associated with an [redacted] in 6MWT compared to SoC, although based on Figure 1, this is unlikely to be statistically significant. In addition, given the variability in the observed data for ESA reported in Figure 1, the ERG is concerned that a simple linear extrapolation has been assumed for SoC. Also, as reported above please note that the comparison between ESA and SoC is naïve and so caution should be taken in drawing any conclusions from the data.

Figure 1. Six-minute walk test (6MWT) distance over time by trial history vs untreated patients in the MOR-001 study (Reproduced from CS, Figure 18)

MOR-001 data is based on [redacted]

Note: All available assessments were included for each patients at each time point.

3.3.1.2 6MWT - MOR-005 QW-QW results

The results of MOR-005 QW-QW for change in 6MWT from baseline were more favourable in the MPP population compared to the ITT population, although both demonstrated a statistically significant improvement for ESA compared to SoC in MorCAP2 and MorCAP1, respectively ($p<0.05$, Table 20). The results of both the ITT and MPP MOR-005 QW-QW analyses suggest the greatest improvement in 6MWT is between baseline and week 24. From 24 weeks up until 120

weeks (2 years), the ERG considers the data suggest the mean 6MWT distance remains reasonably stable (Table 20 and CS, Figure 33). Between 120 weeks and [redacted] weeks there is a [redacted]. The ERG therefore considers it would be beneficial to see a complete case analysis for these data from MOR-005 in order to be able to observe the changes in 6MWT in the same patient cohort.

As discussed in Section 3.2.1, the ERG has included the data from both the CSR of MOR-005 (ITT N=[redacted]) and the CS (ITT N=56). The ERG considers N=[redacted] to be the most appropriate for analysing the long term data from MOR-005 but the ERG is concerned why [redacted] (Table 20).

The ERG notes that the baseline 6MWT in MOR-005 ITT QW-QW (209.4 m [CS]) is [redacted] than that in the Ex-Trial population of the MAA ([redacted] m) [redacted] than that of the ERT-Naïve MAA population ([redacted] m) and there is [redacted] improvement in 6MWT at [redacted] in the MAA patients compared to baseline (MOR-005 ITT QW-QW [CS] = 30.7 m and 32.0 m; MAA Ex-Trial = [redacted]; MAA ERT-Naïve = [redacted] m and [redacted] m; respectively). However, it should be noted that these are naïve comparisons and should not be used for drawing definitive conclusions as they may be subject to bias.

Table 20. Change from baseline in 6MWT in the ITT QW-QW population from MOR-005 and in untreated patients from MorCAP

Timepoint	ITT QW-QW as reported in the CSR (N=[redacted])	ITT QW-QW as reported in the CS (N=56)	MorCAP1 (N=97)	MPP QW-QW as reported in the CSR (N=[redacted])	MPP QW-QW as reported in the CS (N=43)	MorCAP2 (N=79)
Baseline 6MWT (m)						
• Mean (SD)	[redacted]	209.4 (71.8)	207.8 (84.3)	[redacted]	208.8 (73.2)	210.4 (83.4)
• Median	[redacted]	218.7	220.5	[redacted]	226.9	221.5
Mean change (SD/SE) from baseline at timepoint (m)						

• 24 weeks	[redacted]	37.2 (SE 7.9)	NR	[redacted]	41.5 (SE 9.1)	NR
• 36 weeks	[redacted]	42.2 (SE 7.1)	NR	[redacted]	44.4 (SE 8.3)	NR
• 72 weeks	[redacted]	30.7 (SE 10.2) (N=54)	NR	[redacted]	37.5 (SE 11.0) (N=43)	NR
• 120 weeks	[redacted]	32.0 (SE 11.3) (N=51)	NR	[redacted]	39.9 (SE 10.1) (N=41)	NR
• [redacted] weeks	[redacted]	NR	NR	[redacted]	NR	NR
Least square mean change (SE)[a] from baseline at timepoint (%)						
• 72 weeks (year 1)	NR	31.8 (10.86) (N=54)	–8.4 (8.91) (N=80)	NR	38.5 (11.02) (N=43)	–6.7 (8.78) (N=67)
• 120 weeks (year 2)	NR	32.1 (11.75) (N=51)	–16.4 (12.50) (N=40)	NR	39.0 (11.32) (N=41)	–21.9 (12.30) (N=27)
p value[b] QW-QW versus MorCAP 1 or 2 as appropriate at 72 weeks	NR	0.0046	–	NR	0.0016	–
p value[b] QW-QW versus MorCAP 1 or 2 as appropriate at 120 weeks	NR	0.0050	–	NR	0.0003	–

[a] The measure of variance is not specified in the company submission. Based on other values reported in the table in the company submission (Table 37), the ERG has assumed the measure of variance to be SE.

[b] t-test and repeated measures ANCOVA model comparing treated QW-QW versus MorCAP1 population.

Abbreviations: 6MWT, 6-minute walk test; ANCOVA, Analysis of covariance; ERG, Evidence Review Group; ITT, intention to treat; m, metres; MPP, modified per protocol; SD, standard deviation; SE, standard error.

3.3.1.3 *6MWT – age subgroup analysis*

The company reported that 6MWT was stable or numerically improved regardless of age at treatment initiation (Clarification response A16, Figures 1 and 2). However, the ERG notes that the age subgroups combine patients from the Ex-Trial and ERT-Naïve subgroups and are restricted to subgroups aged <18 years and ≥18 years. The ERG considers the data suggest the baseline 6MWT is [redacted] in the subgroup of patients ≥18 years old, although [redacted] from baseline over time. The ERG notes that the percentage improvement from baseline to last follow-up is [redacted] in the patients ≥18 years compared to those <18 years ([redacted]% compared to [redacted]%, respectively, with mean treatment duration of [redacted] years).

The ERG also notes that subgroup analyses in MOR-005 reported 6MWT improvements was not impacted by baseline 6MWT distance, use of a walking aid, or age although no numerical results were reported in the CS.[60]

3.3.1.4 *3-minute stair climb test (3MSCT) - MOR-005 QW-QW results*

The ERG notes that 3MSCT data were not collected in the MAA but data were reported in the CS from MOR-005. The results for 3MSCT were in keeping with those for 6MWT, in that change from baseline in 3MSCT was statistically significantly increased with ESA compared to SoC at both year 1 and year 2 for the ITT QW-QW population from MOR-005 when compared to MorCAP1 (p<0.05, Table 21).

Table 21. Change from baseline in 3MSCT in the ITT QW-QW population from MOR-005 and in untreated patients from MorCAP

Timepoint	ITT QW-QW as reported in the CSR (N=[redacted])	ITT QW-QW as reported in the CS (N=56)	MorCAP1 (N=88)	MPP QW-QW as reported in the CSR (N=[redacted])	MPP QW-QW as reported in the CS (N=43)	MorCAP2 (N=74)
Baseline 3MSCT (stairs per minute)						

• Mean (SD)	[redacted]	30.1 (16.2)	31.3 (17.5)	[redacted]	31.3 (16.2)	32.2 (17.8)
• Median	[redacted]	30.7	29.3	[redacted]	31.3	30.6
Mean change (SD) from baseline at timepoint (m)						
• 24 weeks	[redacted]	NR	NR	[redacted]	NR	NR
• 36 weeks	[redacted]	NR	NR	[redacted]	NR	NR
• 72 weeks	[redacted]	NR	NR	[redacted]	NR	NR
• 120 weeks	[redacted]	NR	NR	[redacted]	NR	NR
•168 weeks	[redacted]	NR	NR	[redacted]	NR	NR
Least square mean change (SE)[a] from baseline at timepoint (%)						
• 72 weeks (year 1)	NR	5.0 (1.71) (N=54)	–0.7 (1.46) (N=80)	NR	5.5 (1.85) (N=43)	0.5 (1.51) (N=67)
• 120 weeks (year 2)	NR	5.3 (2.10) (N=51)	–1.1 (2.27) (N=40)	NR	6.2 (2.24) (N=41)	–1.2 (2.39) (N=27)
p value[b] QW-QW versus MorCAP 1 or 2 as appropriate at 72 weeks	NR	0.0129	–	NR	0.0375	–
p value[b] QW-QW versus MorCAP 1 or 2 as appropriate at 120 weeks	NR	0.0407	–	NR	0.0236	–

[a] The measure of variance is not specified in the company submission. Based on other values reported in the table in the company submission (Table 37), the ERG has assumed the measure of variance to be SE.

[b] t-test and repeated measures ANCOVA model comparing treated QW-QW versus MorCAP1 population.

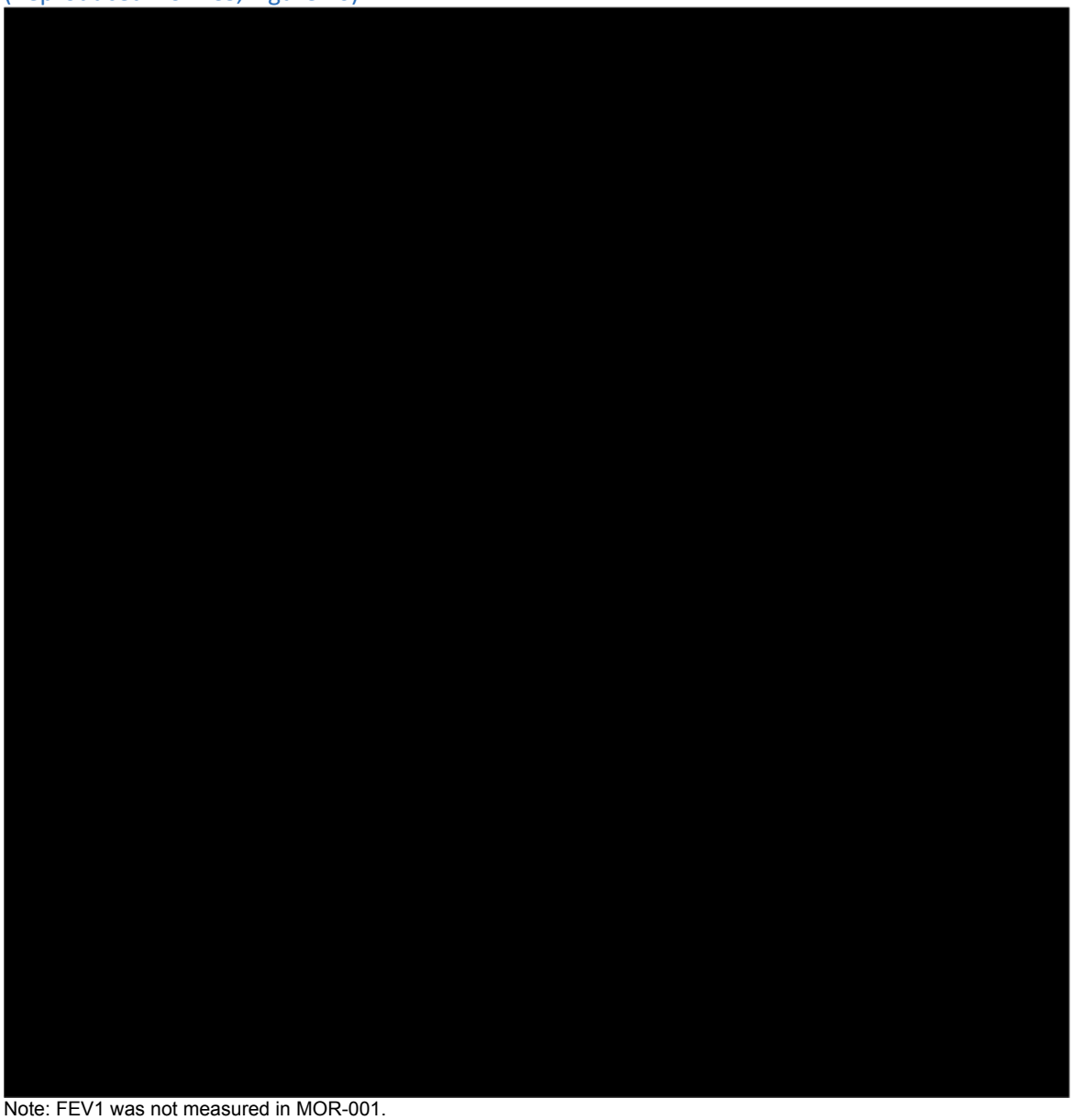
Abbreviations: 3MSCT, 3-minute stair climb test; ANCOVA, Analysis of covariance; ERG, Evidence Review Group; ITT, intention to treat; m, metres; MPP, modified per protocol; SD, standard deviation; SE, standard error.

3.3.2 Pulmonary function

3.3.2.1 FVC and FEV1 - MAA

The ERG considers it difficult to draw conclusions from the lung function results for FVC and FEV1 in the MAA over time as the results for the [redacted] (Figure 2). The ERG notes that the natural history data from MOR-001 suggest a [redacted]

Figure 2. Change in FVC (A) and FEV_1 (B) over time with comparison to MOR-001 natural history (Reproduced from CS, Figure 20)



Note: FEV1 was not measured in MOR-001.
Note 2: All available assessments were included for each patients at each time point.
Note 3: Results for ERT-Naïve patients may be affected by data being available in only 2 patients (year 4), with several missing data.

3.3.2.2 FVC and FEV1 - MOR-005

Pulmonary function outcomes were not reported for the MOR-005 ITT QW-QW subgroup in the CS. However, results for the MOR-005 MPP QW-QW and for the MOR-005 QW-QW ITT were provided in the CQ response. The ERG notes that FVC increased from baseline by 8.4% at 72 weeks and then decreased to 5.6% at 120 weeks (CQ response, Table 11). The ERG considers the results for FEV1 reported in CQ response, Table 11 likely to be

[redacted] The results from the CSR suggest [redacted]

3.3.2.3 FVC and FEV1 age subgroup analysis

In the subgroup data from the MAA by age for patients with both baseline and follow-up data, the mean FVC and FEV1 demonstrated [redacted] from baseline in patients aged <18 years old ([redacted]% and [redacted]%, respectively; CS, Table 40 and Figure 21). [redacted]

3.3.3 Urinary keratan sulfate (uKS)

3.3.3.1 uKS - MAA

Mean uKS for patients in the MAA demonstrated a [redacted] from baseline to last follow-up (CS, Figure 15):

- For ERT-Naïve patients ([redacted]) the mean change in uKS was -[redacted]) and,
- For Ex-Trial patients ([redacted]) the mean change in uKS was [redacted]).

In terms of change over time for uKS, mean uKS [redacted] over the first year of treatment with ESA in both Ex-Trial and ERT-Naïve patients, [redacted] (Figure 3). The ERG is unsure why uKS levels for [redacted].

Figure 3. MAA mean urinary keratan sulfate (uKS) over time (Reproduced from CS, Figure 14)

3.3.3.2 uKS - MOR-005 QW-QW

The mean change in uKS from baseline to weeks 72 (1 year) and 120 (2 years) showed a statistically significant reduction with ESA in the MOR-005 ITT QW-QW population compared to SoC in MorCAP1 ($p<0.0001$, Table 22). The ERG notes that the mean change in MOR-005 in uKS following treatment with ESA is

. The ERG considers a complete case analysis of patients reaching week 168 would be beneficial to help confirm they long term impact of ESA on uKS.

Table 22. Percent change from baseline in urinary keratan sulphate in the QW-QW population from MOR-005 and in untreated patients from MorCAP1 and MorCAP2

Timepoint	ITT QW-QW as reported in the CSR (N=)	ITT QW-QW as reported in the CS (N=56)	MorCAP1 (N=97)	MPP QW-QW as reported in the CSR (N=)	MPP QW-QW as reported in the CS (N=43)	MorCAP2 (N=79)
Baseline uKS (microgram/mg)						

• Mean (SD)	[redacted]	27.2 (14.2)	33.5 (25.6)	[redacted]	24.9 (13.13)	32.2 (27.4)
• Median	[redacted]	25.0	30.7	[redacted]	23.4	27.6
Percent change (SD) from baseline at timepoint (%)						
• 24 weeks	[redacted]	NR	NR	[redacted]	NR	NR
• 36 weeks	[redacted]	NR	NR	[redacted]	NR	NR
• 72 weeks	[redacted]	NR	NR	[redacted]	NR	NR
• 120 weeks	[redacted]	NR	NR	[redacted]	NR	NR
•168 weeks	[redacted]	NR	NR	[redacted]	NR	NR
Least square mean change (SE)[a] from baseline at timepoint (%)						
• 72 weeks (year 1)	NR	–57.6 (9.06) (N=51)	32.7 (7.64) (N=72)	NR	–57.5 (11.16) (N=41)	29.6 (9.30) (N=59)
• 120 weeks (year 2)	NR	–63.8 (6.60) (N=47)	5.6 (6.98) (N=23)	NR	–63.8 (7.47) (N=38)	6.2 (8.46) (N=13)
p value[b] QW-QW versus MorCAP 1 or 2 as appropriate at 72 weeks	NR	<0.0001	–	NR	<0.0001	–
p value[b] QW-QW versus MorCAP 1 or 2 as appropriate at 120 weeks	NR	<0.0001	–	NR	<0.0001	–

[a] The measure of variance is not specified in the company submission. Based on other values reported in the table in the company submission (Table 37), the ERG has assumed the measure of variance to be SE.

[b] t-test and repeated measures ANCOVA model comparing treated QW-QW versus MorCAP1 population.

Abbreviations: ANCOVA, Analysis of covariance; ERG, Evidence Review Group; ITT, intention to treat; MPP, modified per protocol; SD, standard deviation; SE, standard error; uKS, urinary keratan sulphate.

3.3.3.3 uKS age subgroup analysis

Subgroup analysis by age for uKS in patients in the MAA suggests that uKS levels were [redacted] in patients under 18 years old from baseline and at all subsequent timepoints compared to in patients aged ≥ 18 years. The ERG notes that there was a [redacted] between baseline and year 1 in uKS levels in both age subgroups [redacted].

3.3.4 Left ventricular ejection fraction (LVEF)

The ERG notes that LVEF was [redacted] but for [redacted] during the MAA data collection period (CS, Figure 22). No data on LVEF was presented in the CS for MOR-005 or MOR-001, although the ERG notes from the CSR for MOR-005 that [redacted]. The ERG is unsure whether any data for cardiac outcomes are available for MOR-001 and due to time constraints was unable to fully review [redacted].

3.3.5 Height, growth rate and weight

Height and growth rate were not reported in the CS for the MAA patients and weight was only reported by age subgroup for patients in the MAA. The ERG notes that for patients aged ≥ 18 years there was a [redacted] in weight over time [redacted] (CS, Figure 17). The ERG notes that an increase in weight over time for children would be consistent with growth but is unsure how the changes in weight for the patients in the MAA relate to expected changes in growth for healthy children or for those with MPS IVA who are receiving SoC.

There were no data presented in the CS on height, growth rate or change in weight during MOR-001 or MOR-005, although the ERG notes from the CSR of MOR-005 that [redacted].

3.3.6 MPS-HAQ (Activities of daily living)

3.3.6.1 MAA

Comparison of MPS-HAQ data from the MAA for ESA with MOR-001 data on SoC showed [redacted] (CS, Table 41 and Figures 23 and 24). The company reported that the improvements in MPS-HAQ scores were mainly driven by improvements in the ERT-Naïve subgroup of the MAA and in the subgroup of Ex-Trial patients who started treatment in MOR-002.

3.3.6.2 MOR-005

The ERG notes that MPS-HAQ data were also available from MOR-005 and considers them to be generally in keeping with the results seen from the MAA.

3.3.7 Wheelchair use

3.3.7.1 MAA

At last follow-up (mean treatment duration [redacted] years) there was a [redacted] proportion of patients in the [redacted] wheelchair categories in the ERT-Naïve subgroup of the MAA compared to baseline. [redacted] the natural history cohort of patients (2 years follow-up) suggesting

*

[redacted]

Figure 4. Patients showing stability, decline, or improvement in wheelchair

status over time versus baseline (based on MPS-HAQ Mobility Q33 and Q33a regarding wheelchair use; Reproduced from CS, Figure 25)

[redacted]

[redacted]

[redacted]

3.3.7.2 MOR-005

The ERG considers that the results for change in wheelchair use from baseline to 120 weeks (Year 2) in MOR-005 suggest a possible worsening for patients starting in the no wheelchair use category, a potential improvement for patients in the always use wheelchair category and no clear benefit for those in the occasional use wheelchair category. The ERG notes that the company presents the results alongside data from MOR-001 in the CS (CS, Table 54) but the ERG is unsure whether this is the full ITT population and which population the MOR-001 data originate from.

The ERG considers the wheelchair change from baseline data from MOR-005 suggest a similar treatment effect at 2 years to that from MOR-001 for patients in the no wheelchair and occasional wheelchair groups at baseline. Potentially there is a benefit with ESA compared to SoC for the always use wheelchair patients at baseline, albeit based on a difference of just one additional patient moving from always to occasional use in MOR-005 compared to in MOR-001. The ERG also notes that ESA was given open-label by week 120 of MOR-005 and that similar issues to those in the MAA of wheelchair use being assessed subjectively and small patient numbers, also apply to MOR-005. The ERG therefore considers the wheelchair use change from baseline data to be inconclusive.

Table 23. Change in wheelchair use after 120 weeks of treatment with 2.0 mg/kg/QW of ESA compared to MOR-001 (Adapted from CQ response, Table 22)

Wheelchair health state at week 120 (2 years)	Wheelchair health state at Baseline					
	MOR-005	MOR-001	MOR-005	MOR-001	MOR-005	MOR-001
	No WC		Occasional WC		Always WC	
No WC	21 (80.8%)	30 (78.9%)	3 (13.6%)	1 (3.4%)	0 (0%)	0 (0%)
Occasional WC	4 (15.4%)	8 (21.1%)	16 (72.7%)	21 (72.4%)	2 (40%)	1 (16.7%)
Always WC	1 (3.8%)	0 (0%)	3 (13.6%)	7 (24.1%)	3 (60%)	5 (83.3%)
Total	26 (100%)	38 (100%)	22 (100%)	29 (100%)	5 (100%)	6 (100%)

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

3.3.8 *Other patient-reported outcomes in the MAA*

The MAA captured data on EQ-5D-5L utility score, pain severity and depressive symptoms (CS, Figures 26 to 29). The ERG notes that it is reported by the company that these all remained stable over time, although the data for Ex-Trial patients maybe confounded as their baseline was assessed at entry to the MAA if they had no previous assessments.

3.3.9 *Antibody titres (MAA)*

The company reported that immunogenicity data were collected during the MAA and that they considered it not to be possible to correlate the level of antibody titres to treatment adherence. The ERG notes that antibody titres are presented over time by age subgroup (<18 years and ≥ 18 years) split by patients on and off treatment (CS, Figure 30). The ERG considers that the data shows [redacted] but also notes that there are [redacted] of patients in each of the analyses beyond baseline with a maximum of [redacted] patients informing any single data point.

3.3.10 *Mortality*

There were no deaths in the QW-QW arms of MOR-004 or MOR-005, or in the MAA until the data cut-off of [redacted] The company reported that one patient in the MAA has died since the [redacted] data cut, but they are not aware of the reason or the treatment group of the patient.

No data on mortality were available to the ERG for MOR-001.

3.3.11 Adverse effects

Data on adverse effects associated with use of ESA at a dose of 2.0 mg/kg/week are derived from six studies evaluating a total of 222 children, adolescents and adults receiving the optimum dose, with treatment duration ranging from 1 week to 100.1 weeks. The mean total ESA dose per recipient was 56.8 (SD ± 54.89) mg/kg.[61] The ERG notes that adverse effects do not feature in the economic model.

The most common adverse effects experienced with ESA, affecting more than 1 in 10 recipients, are infusion-related reactions, including headache, nausea, vomiting, and fever (Table 24). Infusion-associated reactions typically occurred within one day of the start of the infusion, and were usually mild or moderate in severity. Infusion-related reactions were more frequent in the first 12 weeks of treatment, with minimal fluctuation in the frequency of adverse effects in the longer term (Table 24). No adverse effect led to the permanent discontinuation of the treatment and no treatment-related death has been reported.

Serious adverse effects and hypersensitivity AEs are rare. In MOR-005, one patient experienced anaphylaxis (grade 4 event) and a second had haematuria (grade 2 event). Most serious adverse effects are related to the underlying disease, including disease progression, or to intravenous administration of ESA. The company comments that real-world results from the MAA and from the MARS registry support the safety profile of ESA, with no new adverse effects of concern identified. However, the ERG notes that safety data were not routinely collected for patients in the MAA and no numerical safety data are reported.

Table 24. Common adverse effects associated with elosulfase alfa 2.0 mg/kg/week[61]

Adverse effect	Duration of treatment with elosulfase alfa (weeks)					
	1–12 (N=222)	13–24 (N=121)	25–36 (N=98)	37–48 (N=82)	>48 (N=52)	Total (N=222)
Reported at least one adverse effect	170 (76.6%)	97 (80.2%)	73 (74.5%)	66 (80.5%)	42 (80.8%)	171 (77.0%)
Vomiting	55 (24.8%)	23 (19.0%)	13 (13.3%)	14 (17.1%)	15 (28.8%)	77 (34.7%)
Pyrexia	46 (20.7%)	28 (23.1%)	20 (20.4%)	13 (15.9%)	14 (26.9%)	76 (34.2%)

Headache	52 (23.4%)	24 (19.8%)	14 (14.3%)	14 (17.1%)	13 (25.0%)	75 (33.8%)
Cough	29 (13.1%)	14 (11.6%)	7 (7.1%)	5 (6.1%)	9 (17.3%)	52 (23.4%)
Nausea	32 (14.4%)	12 (9.9%)	6 (6.1%)	10 (12.2%)	4 (7.7%)	43 (19.4%)
Diarrhoea	22 (9.9%)	7 (5.8%)	4 (4.1%)	4 (4.9%)	9 (17.3%)	37 (16.7%)
Pain in extremity	19 (8.6%)	5 (4.1%)	8 (8.2%)	9 (11.0%)	5 (9.6%)	36 (16.2%)
Arthralgia	18 (8.1%)	11 (9.1%)	9 (9.2%)	5 (6.1%)	5 (9.6%)	35 (15.8%)
Abdominal pain	21 (9.5%)	7 (5.8%)	5 (5.1%)	4 (4.9%)	2 (3.8%)	33 (14.9%)
Nasopharyngitis	11 (5.0%)	13 (10.7%)	6 (6.1%)	5 (6.1%)	7 (13.5%)	33 (14.9%)
Fatigue	15 (6.8%)	8 (6.6%)	5 (5.1%)	8 (9.8%)	5 (9.6%)	31 (14.0%)
Oropharyngeal pain	17 (7.7%)	9 (7.4%)	6 (6.1%)	7 (8.5%)	3 (5.8%)	31 (14.0%)
Upper respiratory tract infection	11 (5.0%)	13 (10.7%)	11 (11.2%)	6 (7.3%)	3 (5.8%)	30 (13.5%)
Upper abdominal pain	15 (6.8%)	5 (4.1%)	6 (6.1%)	3 (3.7%)	6 (11.5%)	25 (11.3%)
Rash	7 (3.2%)	10 (8.3%)	5 (5.1%)	5 (6.1%)	6 (11.5%)	23 (10.4%)

3.4 Correlations between measures in the MAA

The company conducted a pairwise correlation to assess for correlation across the clinical measures and patient reported outcomes. The ERG notes that the data from ERT-Naïve and Ex-Trial patients were combined and the company reported that listwise deletion was used to handle missing data. There were 32 patients in the final analysis.

The results of the correlation assessment are summarised in Table 25. Of particular note, FVC and FEV1 were significantly positively correlated and FVC was significantly negatively correlated with 6MWT (i.e. patients who deteriorate in 6MWT from baseline also worsen in lung function). However, as discussed previously the ERG has concerns with the way in which data from the MAA have been analysed by the company and therefore the ERG recommends caution in drawing any conclusions from these correlations.

Table 25. Pearson's correlations between clinical measures change from baseline (Reproduced from CS, Table 42)

Variables	6MWT	FVC	FEV1	uKS	EQ-5D	MPS-HAQ (Mobility domain)	MPS-HAQ (Self-care domain)
6MWT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
uKS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPS-HAQ (Mobility domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPS-HAQ (Self-care domain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Values in bold are different from 0 with a significance level alpha = 0.05.

Abbreviations: 6MWT, 6 minute walk test; EQ-5D, EuroQol 5 dimensions, 5 levels; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MPS-HAQ, MPS Health Assessment Questionnaire; uKS, urinary keratan sulphate.

3.5 Critique of the PSM

[redacted]

3.2

3.2

Table 26

[redacted]

3.2 [redacted]

[redacted]

Table 26. Results of PSM analyses of ESA versus SoC for 6MWT (Reproduced from Company PSM report)

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3.6 ERG exploratory analysis for 6MWT and FVC

As discussed previously, the ERG considers a complete case analysis to be a more appropriate method of analysis for the clinical data and so the ERG has conducted an exploratory analysis using data from the MAA as an illustrative example to demonstrate the impact on the results of such an analysis compared to the company's current approaches. The ERG has only conducted an analysis of 6MWT and FVC using the MAA ERT-Naïve subgroup as these outcomes are deemed by the ERG to potentially be of most relevance to the economic model and the ERT-Naïve subgroup of the MAA comprises patients who have received the 'correct' dose of ESA from treatment initialisation. However, the ERG notes that potentially patients from the Ex-Trial subgroup could also be included, although the ERG is unsure which patients had received the standard ESA dose from their original trial baseline and so was unable to include them in the ERG analysis. The ERG analysis is also subject to the ERG's interpretation of the IPD supplied by the company and so there is also a concern that there may be errors in the ERG interpretation of the data provided by the company.

The ERG has selected a three year timepoint for its complete case analysis and thus required all patients to have data available at baseline and each year up to and including 3 years. The ERG selected 3 years as it considers it to be the best compromise of number of patients informing the analysis for the longest period of time to inform the efficacy of ESA.

The results from the ERG's exploratory analysis are presented in Table 27 alongside the results presented by the company from their analyses at the equivalent timepoints as reported in Figure 1 and Figure 2. The ERG considers the company analysis comprises all patients followed longitudinally with data available at the timepoint analyses and missing patients are omitted from the analysis but may be included at later timepoints. It should be noted that the ERG has

used rounding to the nearest timepoint to enable the inclusion of as many patients as possible in the analysis, for example, patients with data at 20 months and will be included in the year 2 analysis if data are not at 24 months, etc. In addition, the ERG has used only assessments at exactly the correct timepoint if a patient had additional assessments, for example, where there was a 20 month and 24 month assessment of 6MWT, the ERG uses only the 24 month assessment to inform 2 years. As discussed previously, the ERG is concerned that the company has used [redacted] and where a patient has an assessment at the correct timepoint as well as assessments several months before or after the company may have used [redacted].

While the ERG recommends caution in drawing conclusions from the company's results, the ERG also considers it important to note that [redacted]. The results from the ERG analyses also show [redacted] compared to the company results. In both the analysis of 6MWT and FVC, the ERG results suggest [redacted]. Unfortunately due to time constraints and concerns regarding the coding of the data supplied to the ERG for MOR-001, the ERG was unable to conduct equivalent complete case analyses for SoC and so the ERG is unable to draw conclusions on the impact of ESA compared to SoC.

Table 27. ERG's exploratory complete case analysis for 6MWT and FVC in MAA ERT-Naïve patients (3-year timeframe)

	Baseline	Year 1	Year 2	Year 3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute walk test; CS, company submission; ERG, Evidence Review Group; FVC, forced vital capacity.

3.7 Conclusions of the clinical effectiveness section

The ERG has numerous serious concerns with the clinical effectiveness evidence presented for assessment despite the overwhelming volume of information supplied by the company. Firstly, the ERG is concerned about the lack of a clinical SLR to identify data on SoC, although data were provided from the company's own natural history study MOR-001. The ERG's clinical experts didn't report knowledge of any other studies of relevance, but the ERG considers an SLR should nevertheless have been conducted by the company.

The ERG considers it likely that no relevant evidence for ESA was excluded for the key outcomes included in the economic model based on the eligibility criteria used in the company's SLR. However, the ERG considers the CS lacked clarity in terms of the number of studies included. The ERG also considers the company's handling of the ESA studies, following their inclusion in the SLR, to lack clarity, and considers it to be uncertain whether all available results are reported in the CS. In addition, the ERG notes that not all studies had quality assessments conducted and again the rationale for this is unclear.

Of the included ESA studies in the company's SLR, the ERG considers the QW-QW subgroup of MOR-005, and the MAA to be of the most relevance to the NICE final scope. This is because the MAA reflects treatment with ESA of UK patients since the NICE appraisal of ESA in HST2 and the QW-QW subgroup of MOR-005 comprises patients who have received the recommended EU licensed dose of ESA from the start of treatment. The ERG notes that the clinical data from MOR-005 at the time of HST2 were from an interim analysis at 72 weeks of ESA treatment, whereas the study has now completed and data for up to 264 weeks follow up are available. The MAA and MOR-005 collected outcome data on 6MWT and lung function, which the ERG's clinical experts reported were key clinical outcomes of relevance. The ERG therefore focussed its critique on the MAA and MOR-005 QW-QW along with MOR-001 to inform SoC.

As discussed in Sections 3.2.1 to 3.2.3, the ERG is concerned with the company's current analyses of the data from MOR-001, MOR-005 QW-QW and the MAA and considers a complete case

analysis would be a more appropriate method of analysis of the data in each of the studies. The ERG considers a complete case analysis would be particularly beneficial for MOR-001 and the MAA but also considers a complete case analysis for MOR-005 would enable more robust conclusions to be drawn from the longer term follow-up data that are available, for example, week [redacted]. A complete case analysis would ensure a consistent cohort of patients are followed up from baseline at each timepoint (year) for each individual outcome. In the current analyses, patients may be missing from an analysis at one timepoint but be included in the baseline and later timepoints. Given the heterogeneity in the disease presentation of MPS IVA, the ERG considers it likely that baseline and subsequent assessments could be skewed by the extremely different outcomes of individual patients. The ERG is thus concerned that this variability in baseline and outcome assessments between individual patients could lead to an over or under estimation of any treatment effect resulting from ESA or SoC. The ERG therefore considers it important to have a consistent cohort of patients in order to draw any conclusions on changes over time with ESA and SoC.

Nevertheless, the ERG also acknowledges that a complete case analysis has limitations as we do not know the characteristics of the patients who are discarded from the analysis due to being 'incomplete' cases and they are unlikely to be missing at random from the analysis.

In addition to the complete case analysis, the ERG considers it important that the company use consistent definitions of timepoints for the analysis of data from each study. For example, for 1-Year post-baseline, only data between 6 and 17 months (i.e. 0.5 to <1.5 years) post-baseline should be utilised and where possible, the nearest assessment to 1-Year post-baseline should be used. The ERG is particularly concerned about the suitability of the data for SoC that is originating from MOR-001 because the data at 1-Year post-baseline could in fact be 2 or even 3 calendar years from baseline given the date of change in study design from cross-sectional (2008) to longitudinal (2011) in MOR-001. The ERG also identified some potential discrepancies in the outcome data reported for MOR-005 depending on the source used and considers the correct results for the ITT population from MOR-005 (N = 56) need clarifying.

In summary, the ERG does not consider the current data analyses of clinical outcomes suitable to draw conclusions on the efficacy of ESA compared to SoC. The ERG considers a complete case analysis would be beneficial in addressing issues relating to the lack of coherent data sets in the

current analyses and that consistent definitions of timepoints are required in all analyses to enable reliable comparisons between ESA and SoC.

3.8 ERG recommendations for analyses of the clinical data

The ERG considers an analysis comparing the full ITT population of MOR-005 QW-QW and the patients from MorCAP1 should be conducted and a further analysis of the patients from the MAA and the full MOR-001 population. In both instances, complete case analyses should be conducted for consistency, and then the feasibility of subsequent PSM analyses should be explored. The ERG considers the clinical data in the complete case analyses should be analysed to ensure consistent methods are used to assign clinical data to analyses at different timepoints. For example, data from only 0.5 to <1.5 years post-baseline should be used to inform the 1 year change from baseline analysis. In addition, only data collected at the nearest time to that defined as the timepoint of the analysis should be used. For example, for Year 1 analyses, the data collected from the assessment closest to 12 months post-baseline should be used.

Based on the clinical data, the ERG considers it likely that the complete case analysis of the MOR-005 QW-QW data for ESA is likely to result in a larger sample size compared to that of a complete case analysis of the MAA data. The ERG, therefore, recommends that the results for ESA from the revised analyses of MOR-005 QW-QW are used to inform the economic model and for SoC the complete case analysis of MorCAP1 is used. However, if there are sufficient data the ERG also considers the use of the MAA data could be used in a scenario analysis. Where the MAA data are used, the ERG considers the full MOR-001 population should be used rather than only the MorCAP1 subgroup.

The ERG notes that most of the current analyses of the MAA data have been divided into separate analyses of the ERT-Naïve and Ex-Trial patients. The ERG considers that the use of complete case analyses and consistent definition of timepoints in the analyses may enable a single analysis of the MAA data. However, the ERG also notes that there are [redacted] Ex-Trial patients ([redacted]%) who have not received the 2.0 mg/kg/QW ESA dose approved in the marketing authorisation from the start of their original trial. The current analyses of the data from these patients uses their baseline from the start of their original clinical trial and the ERG considers this to potentially impact on the reliability of the results from the Ex-Trial cohort of the MAA. The ERG therefore considers a further sensitivity analysis of the MAA study should be conducted

using a complete case analysis and excluding the patients who have not received the 2.0 mg/kg/QW ESA dose from baseline of their original trial.

4 Cost effectiveness

During the clarification stage (and later in the review process), the company provided the ERG with individual patient-level data (IPD) for the two pivotal studies underpinning the economic analysis – the managed access agreement (MAA); and the MOR-001 study. The ERG's investigation of the IPD data yielded different clinical outcomes for both elosulfase alpha and standard of care when compared to those reported in the CS and used in the company's model. This issue is discussed in detail in Section 3.

Furthermore, as discussed in Section 3, the ERG's investigation led to the conclusion that the company's analysis of the raw MOR-001 and MAA data was flawed. Therefore, the ERG considers that the data used in the economic analysis to estimate the relative treatment effectiveness of elosulfase alpha against standard of care are unfit for decision making.

In the following sections the ERG provides a critique of the company's modelling approach, however, some aspects of the latter cannot be fully analysed until the company clarifies the discrepancies found in the IPD and in the estimates used by the company; and crucially, until the company re-analyses the clinical data included in the model. As discussed in Section 3.8, the ERG concluded that the most robust set of data available to estimate the relative treatment effect of ESA compared to SoC is likely to consist of a complete case analysis using the full ITT population of MOR-005 QW-QW and the patients from Mor-CAP1. This should be followed by an assessment of the feasibility of a subsequent propensity score matching analyses for each outcome. The results from these analyses should be then used in the economic model for ESA and SoC, respectively.

The ERG also recommends that the company considers running a scenario analysis where the MAA is used as the main source of data for the clinical effectiveness of ESA. The ERG recommends that a complete case analysis of the MAA ex-trial population is employed, together with a complete case analysis of MOR-001 (full ITT population). The results from these analyses should be then used in the economic model for ESA and SoC, respectively (see more details in Section 3.8).

4.1 ERG comment on the company's review of cost effectiveness evidence

The company carried out systematic literature reviews (SLRs) in October 2019 to identify existing cost-effectiveness evidence, healthcare resource use and health-related quality of life (HRQoL)

evidence for MPS-IVA patients and their carers. The company included multiple sclerosis terms in their search as a proxy term to capture carer evidence as MPS-IVA is a rare disease.

A summary of the ERG's assessment of the company's SLR approach is presented in Table 28. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 28. Systematic literature reviews overview

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Section 2.1 of the economic analysis, costs and resource use systematic review report	Section 2.1 of Utilities systematic review report	Section 2.1 of the economic analysis, costs and resource use systematic review report	Appropriate. Embase, Medline, Medline in Process/e-publications ahead of print, NHS EED and HTAD, CRD. Grey literature was sourced from the last 2 years of ISPOR International and European conferences (2018/2019), hand searches of previous systematic reviews and cost-utility analysis reference lists, included trials reference lists, CEA registry, RePEc and HTA websites (NICE, SMC, HAS, AWMSG, CADTH). MeSH terms were used, and external advice from an information expert. Search filters, economic filter adapted from Gleville *et al.* 2019, and costs filter from McMaster University Health Information Research Unit filter, with further

				terms added to identify resource use and budget impact analyses. Utility filter adapted from Arber *et al.* 2015 and Arber *et al.* 2017.
Inclusion/exclusion criteria	Table 1 of economic analysis, costs and resource use systematic review report	Table 1 and Table 2 of utilities systematic review report	Table 1 of economic analysis, costs and resource use systematic review report	Appropriate.
Screening	Figure 1 of Economic analysis, costs and resource use systematic review report	Figure 1 of utilities systematic review report	Figure 1of economic analysis, costs and resource use systematic review report	Appropriate.
Data extraction	Section 2.1.2 of economic analysis, costs and resource use systematic review report	Utilities systematic review report	Section 2.2.1 of economic analysis, costs and resource use systematic review report	Appropriate
Quality assessment of included studies	Not performed.	NR	NR	Company indicated they would have used the Drummond checklist had they included any full text modelling studies. Included studies were HTA reports.

Abbreviations: CS, company submission; ERG, evidence review group; HRQoL, health related quality of life; NHS EED, National Health Service Economic Evaluation Database; HTAD, Health Technology Assessment Database; CRD. Centre for reviews and dissemination; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; HTA, Health Technology Assessment; SMC, Scottish medicine consortium; HAS, Haute Autorité de Santé; AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health

The electronic database searches for cost-effectiveness and healthcare resource use evidence (MEDLINE and EMBASE through EMBASE.com) identified 97 abstracts, and the utility searches identified 237 abstracts. The PubMed in progress searches identified seven abstracts for cost-effectiveness and resource use and none for HRQoL. The search of the Cochrane database for HRQoL data identified 37 abstracts.

After title/abstract screening, 23 cost-effectiveness and healthcare resource use studies were included for full-text screening, of which 7 were ultimately included. Hand searching of grey literature identified an additional 11 abstracts. In the utility search, 47 studies were included for full text screening, of which 36 were included, with an additional 10 studies included from the hand-searched grey literature.

No cost-effectiveness studies were identified from the published literature. All included studies were previous HTA reports identified through grey literature searches. It was not stated by the company in their report whether these models were used to inform their submission, but as these were all elosulfase alfa models for MPS-IVA, the ERG notes that they are likely to be earlier versions of the model submitted for this HST.

The HRQoL search identified four new sources of utility data that were used in the model for both patients and their carers (Hendricsz *et al.* 2014a, Hendricsz *et al.* 2014b, Lavery *et al.* 2017 and Lampe *et al.* 2015).

Seven studies were included from the healthcare resource use SLR, but ultimately none of the evidence was used in the company's submission or informed the development of the economic model.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 29 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 29. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.

Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. The company's model adopts a 100-year time horizon.
Synthesis of evidence on health effects	Based on systematic review	Unclear. The company's choice of sources for estimating treatment effectiveness lacks transparency and consistency in the analysis.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The same discount rate was used for both costs and health effects; however, the company's base case uses a 1.5% rate.

Abbreviations: ERG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered by the company included prospective new patients diagnosed with mucopolysaccharidosis type IVA (MPS IVA). In their base case, the company used the ERT-naïve population from the MAA dataset as this was considered to reflect the future population to be eligible for ESA in the UK.

The ERG notes that the ex-trial MAA patients who had previously started elosulfase alpha (ESA) in one of the MOR clinical trials (MOR-002, MOR-006 and MOR-007) entered the MAA as well as some

ex-trial patients from MOR-005. Each of these MOR clinical trials had differing inclusion and exclusion criteria thus comprising of heterogenous populations (see Section 3 for more details).

The ERG is unsure if the company's justification for choosing the ERT-naïve patients as the model population is robust. Even though the ex-trial population in the MAA was not treatment naïve at the beginning of the MAA enrolment, there were baseline data available for these patients in their respective studies. In fact, the CS presented clinical outcomes from baseline of respective MOR studies to end of follow-up in the MAA.

Nonetheless, the ERG notes that the ex-trial patients in the MAA may have originally commenced treatment on different doses or frequencies of ESA to that specified in the EU marketing authorisation and the MAA treatment specification. Furthermore, using the ex-trial MAA population would have introduced additional heterogeneity to the study population (given the different trial entry criteria in the MOR studies – please see Section 3.2). In contrast, treatment naïve patients in the MAA will have received the recommended dose of ESA from the start of their treatment, even though they have shorter follow-up data available. On balance, the ERG concluded that using the ex-trial MAA population to model the ESA arm of the model would have brought little gain in the economic analysis, while introducing additional heterogeneity in the effectiveness data.

In addition, the ERG considers the QW-QW subgroup of MOR-005 to also be of relevance for evaluating ESA outcomes (please see Section 2.3.2). The MOR-005 study included patients who received the recommended EU licensed dose of ESA from the start of treatment and collected outcome data on 6MWT and lung function.

Given the ERG's issues around the methodology needed to analyse the MAA data and resulting sample size, the ERG considers that MOR-005 is the more robust source of data to estimate the effectiveness of ESA in the model (see Section 3.8 for more details).

Finally, the ERG notes that according to clinical expert opinion, the baseline distribution of the population in the economic model across the different wheelchair(WC) categories does not reflect a recently diagnosed population, but a more advanced MPS IVA population. This issue is further discussed in Section 4.2.4.

4.2.3 Interventions and comparators

The intervention included in the economic model was ESA 1 mg/ml concentrate solution administered weekly, at a dose of 2mg/kg. This dose is reflected in the ERT-naïve population used in the model, and also in the QW-QW subgroup of the MOR-005 study.

The comparator specified in the NICE final scope and included in the economic model is established clinical management, or standard of care (SoC) without ESA. The main source of clinical data on established clinical management without ESA used in the economic model is from the company's MOR-001 natural history study.

4.2.4 Modelling approach and model structure

The company used the same Markov structure as that submitted in the original HST2 appraisal of ESA (Figure 5). The model incorporates six mutually exclusive health states, and an absorption state of death, which patients can enter from any other state in the model. The focus of the model is on patients' progression through different WC states.

At the beginning of the model, patients were distributed across the asymptomatic (5% of patients); no use wheelchair (NWC) (40% of patients); sometimes use wheelchair (SWC) (50% of patients); and wheelchair dependent (WCD) (5% of patients) states. Asymptomatic patients could progress to the NWC or the paraplegic states, while NWC patients could progress to SWC or the paraplegic state. Patients in the SWC could either improve their WC dependency and move to the NWC state, or progress to the WCD state. Similarly, patients in the WCD state could improve to SWC, or progress to the end-stage health state.

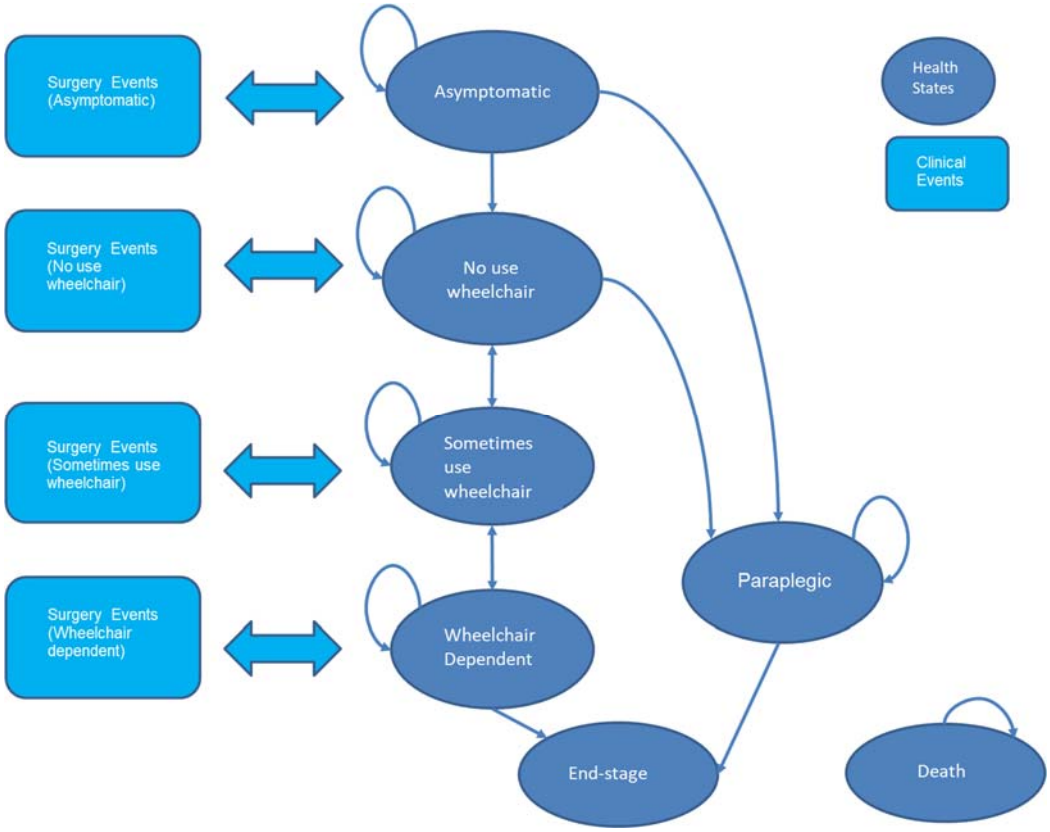
Patients in the paraplegic state could remain in the state or progress to end-stage disease. All patients could remain in their respective WC until death. The different WC dependency states were defined according to the MPS-HAQ questionnaire (question 33 and question 33a) and more details on the definition of each health state is provided on page 328 and 329 of the CS.

Even though surgeries were not included as explicit health states in the model, these were estimated every cycle for the asymptomatic and each WC state in the model.

Patients' movements across health states; survival outcomes; and treatment effectiveness were captured through transition probabilities in the model, which are discussed in Section 4.2.6.

The company assumed that patients never discontinue treatment with ESA in the model as it was reported that there were no discontinuation events observed in the MAA dataset.

Figure 5. Model structure



4.2.4.1 ERG critique

Company's justification for having a wheelchair-based model

The CS reports that the model structure submitted for the HST2 was accepted by the committee. The ERG partially disagrees with this statement as the HST2 evaluation consultation document reports the committee's concerns around having a WC-based model: "*The Committee* [...] *heard from the clinical and patient experts that the categories of wheelchair use in the clinical trials could have been subjective. They emphasised that patients use wheelchairs in different ways, to manage endurance and daily activities according to their individual needs, so the effect of treatment is not necessarily well represented by this measure. Furthermore, patients do not judge their quality of life by how much they are using the wheelchair. The Committee considered that this evidence was*

informative but was mindful of putting too much emphasis on it. " and *"The Committee concluded that the key determinants of mortality are the respiratory and cardiac complications, and that what matters the most to people with the condition is the ability to carry out normal everyday activities with sufficient endurance and without pain or fatigue*."

In light of these conclusions, and during the clarification stage, the ERG asked the company if the HST2 committee's concerns were addressed in the new submission, and asked the company to consider changing the structure of the economic model to place more emphasis on respiratory outcomes, in particular, in the forced vital capacity (FVC) outcome as this is often considered in health technology assessments as moderately well-established predictor of mortality and HRQoL.[62]

As a response, the company conducted various regression analyses using the MAA data ([redacted] patients) to investigate how age; weight; urinary keratan sulphate; the 6-minute walking test (6MWT); WC status; and FVC correlated with EQ-5D results. The company's conclusions were that 6MWT outcomes were consistently significant predictors of EQ-5D scores and WC status (measured by the MPS HAQ questionnaire), while the association of FVC with EQ-5D and WC status was weaker. The company therefore conclude that, "*the most relevant clinical outcome to model MPS IVa wheelchair health states remains the 6MWT*".

The ERG notes that through the analysis provided in their reply, the company has demonstrated that 6MWT is correlated with WC use while FVC may be a weaker predictor of WC use. However, the ERG considers that this does not change its original concern for the choice of WC as a measure of disease progression in the model and notes that the model does not use any data on 6MWT outcomes from the MAA (used in the company's regression analyses to validate their use of WC states in the model). If the company had reasons to consider 6MWT outcomes to be the more relevant predictors of disease progression, the company could have considered building a model which made more use of the 6MWT outcomes available in the MOR-001 and in the MAA and MOR-005 studies.

Furthermore, WC use data from the MOR-001 and the MAA studies are only used in the first year of the economic model, while progression in the subsequent years was based on assumptions for the ESA arm, and on 6MWT and FVC outcomes from MOR-001 for the SoC arm. Therefore, the company had to make further assumptions to link FVC and 6MWT outcomes to the WC states in the model, where the outcome data could have been directly used.

The company also reported that, "*FVC correlates very poorly with HRQoL (EQ5D)*" and that, "*The current model structure, which is driven by wheelchair status correlates strongly with EQ5D*." In response to the ERG's request to having an FVC-based model, the company added that, "… *changing the structure of the model to FVC (from current wheelchair use), may not be associated with health state rewards (EQ5D utility values)*…".

The ERG is concerned with the inconsistency in the company's rationale as the CS (page 347) states that according to Lampe *et al*. 2015 there is a, "… *strong positive correlation between patient's 6MWT and FVC with their HRQoL, as measured by the EQ-5D*".

The ERG concludes that the company's argument for the relationship of 6MWT and FVC outcomes with EQ-5D outcomes is unclear and used by the company to justify contradictory modelling approaches. The company argues a weak correlation between EQ-5D and FVC outcomes to justify having a WC based model; however, it argues for a strong correlation between FVC outcomes and EQ-5D outcomes to apply a utility increment to patients' utilities while receiving ESA (see Section 4.2.8).

Data available to validate having a wheelchair-based model

Literature

The Lampe *et al*. 2015 study (provided by the company to justify the use of ESA-related utility increments) analysed the correlation between 6MWT and FVC (among others) and EQ-5D outcomes in 24 German patients with MPS IVA. The paper concluded that in adults, endurance (6MWT) and pulmonary function (FVC) measures showed a strong and statistically significant correlation with patients' EQ-5D-5L. The study found that an increase of 1m in the 6MWT was associated with an improvement in patients QoL of 0.002 (p-value 0.0016) and an increase in 1L in FVC was associated with an improvement in adults' QoL of 0.205 (p-value 0.0007). The study concluded a strong correlation in adult patients for measures that reflect the patient's endurance/mobility: the 6MWT and the 3MSC test versus EQ-5D-5L and the patient's rating of their ability/strength to walk and climb stairs. Also, hip extension showed a good correlation with EQ-5D-5L.

The study also identified a poor correlation of FVC and 6MWT with EQ-5D-5L outcomes in children, which the authors thought could be explained by differences in disease progression in young patients resulting in a very heterogeneous group. The study also examined the correlation between

the range of movement of various joints (hip, wrist, and shoulder) and patient's EQ-5D-5L outcomes. Children showed stronger correlation between wrist extension and shoulder flexion and EQ-5D-5L than adults. Given these joints' involvement in hand activities, such as writing and playing, the authors concluded that these could be the key determinants for children's EQ-5D-5L.

Additionally, MOR-005 found that impaired respiratory function (measured by FVC and FEV) is one of the leading causes of morbidity and mortality in MPS IVA patients. The study (funded by BioMarin) suggested that ESA slowed down, and partially reversed, the natural progression of respiratory dysfunction associated with MPS IVA over a 2-year period. The ERG therefore, notes again, that a model based on respiratory outcomes would have more appropriately captured disease progression, and possibly the impact of ESA.

MAA data as reported by the company

According to the company's clarification response to question B19, patients' quality of life in the ERT-naïve MAA population changed from baseline to last follow-up, within each WC category. For example, patients in the SWC category ([redacted]) had a utility score of [redacted] at baseline and of [redacted] at end of follow-up ([redacted]). This change in utility within the same WC category implies one of the following: 1) either the WC categories defined by the company are not appropriate to capture all relevant changes in disease progression (because quality of life improves within the same WC state); or 2) the change in quality of life observed within the WC state is not clinically meaningful. Given that the change in EQ-5D score for the SWC state was statistically significant, and the [redacted] increase in the utility score, the ERG argues that the broad definition of the SWC state is unlikely to be sensitive enough to capture disease progression within this state. This reinforces the ERG's view that a WC-focused economic model is unlikely to capture disease progression appropriately.

The ERG investigated the MAA baseline 6MWT and FVC data by WC provided in Table 30. Both FVC and 6MWT measures at baseline provide inconsistent and implausible representations of the modelled WC categories chosen by the company. For example, the company has defined that the mean 6MWT distance at which patients become WC dependent and therefore enter the WCD state in the model (as a result of disease progression) is 46m. Nonetheless, the mean 6MWT at baseline in the MAA population in the WCD category is 55m. For FVC, the company has defined that the mean FVC level at which patients become wheelchair dependent and therefore enter the WCD state in the model (as a result of disease progression) is [redacted]L. Nonetheless, the mean FVC level at baseline in the

ERT-naïve population in the MAA dataset was 4.48L in the WCD state (with the caveat that there was only 1 patient at the beginning of the study in this category).

The ERG recommends that once the MORCAP1 and MOR-005 data are re-analysed (as discussed in Section 3.2.2; Section 3.2.3 and Section 3.3), the same analysis is undertaken, in order to compare the thresholds defined by the company to determine WC use and the clinical data observed in the pivotal studies.

Table 30. Baseline FVC and 6MWT in MAA across WC states – ERG's complete case analysis

	No WC	Sometimes uses WC	Wheelchair dependent
ESA arm (ERT-naïve patients from MAA)			
[redacted]	[redacted]	[redacted]	[redacted]
Mean 6MWT (m)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Mean FVC (L)	[redacted]	[redacted]	[redacted]

The ERG concludes that the company's definition of WC states is poorly correlated with FVC and 6MWT outcomes. This observation further illustrates that the company does not have a robust rationale for having a WC-based model. In fact, given the importance of endurance (measured by the 6MWT) and respiratory outcomes (FVC and FEV1) for patients and for assessing disease progression, the ERG argues that the fact that respiratory outcomes are poorly correlated to the WC states defined by the company is the reason why a WC-based model is unlikely to be appropriate. Change in WC use as the main measure of disease progression in MPS IVA has also been deemed inappropriate by the ERG's clinical experts and was a concern expressed by the HST committee in HST2.

In the CS the company discusses how, based on long-term outcomes from the MAA dataset, positive changes from baseline in 6MWT and FVC outcomes were not an appropriate method to reflect changes in WC dependency as shown in Figure 7 and Figure 8. Based on that observation, the company decided to use WC use as the main modelling outcome. Again, the ERG considers that the exact opposite argument should be made – if endurance (measured through 6MWT) and pulmonary outcomes (measured through FVC) have been deemed the most relevant and sensitive outcomes by patients and clinical experts to assess disease progression and quality of life, **and** have been found to

be poor predictors or poorly correlated with change in WC use, then using WC use as the key outcome in the economic analysis is inappropriate to capture the cost-effectiveness of ESA and is unfit for decision making.

Figure 6. FVC change from baseline compared to 6MWT change from baseline and WC change, ERT Naïve patients, n=19 (Figure 60 CS)

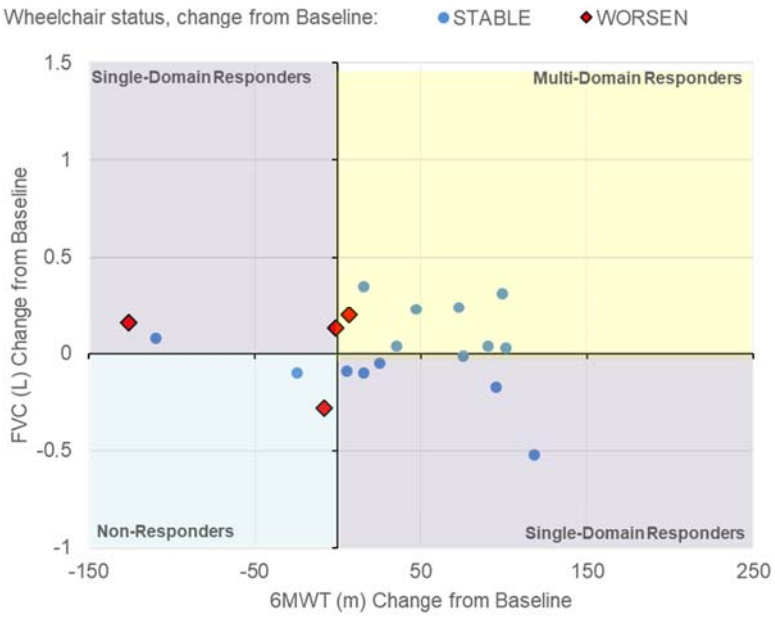
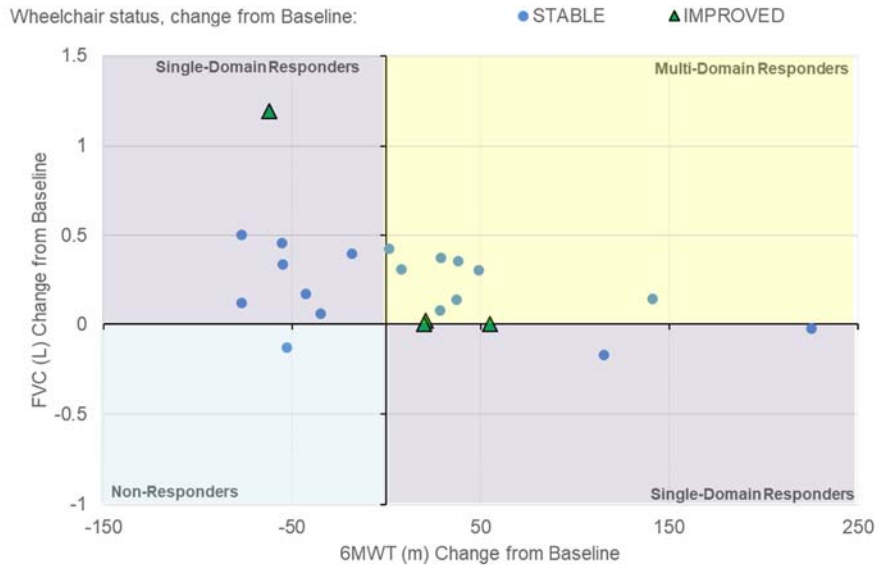


Figure 7. FVC change from baseline compared to 6MWT change from baseline and WC change, ex-trial patients, n=22 (Figure 61 in CS)



Conclusion on company's modelling approach

The ERG concludes that there is evidence to support a strong correlation between endurance and mobility measures (6MWT and 3MSC) and patients respiratory measures (FVC) with patient's EQ-5D-5L/HRQoL. Furthermore, there is also a study pinpointing mobility as the key determinant for HRQoL in patients with MPS IVA. The same study concluded that HRQoL reduces dramatically if patients become WCD, while small increases in mobility leading to less use of a WC greatly improves HRQoL, although the ERG could not ascertain how the different levels of WC dependency were defined or captured in the study.[63]

Given the weak correlation seen in the MAA data between improvements in 6MWT and FVC measures and improvement in WC status (for example, Figure 7 and Figure 8 show that patients' 6MWT in both MAA datasets worsened over time, even for patients who remained on a "stable WC" category throughout the study); the weak standardisation of WC measures in the MPS IVA literature; and the availability of reasonably robust studies establishing the relationship of standardised endurance and respiratory measures (such as the 6MWT and FVC) with patients' QoL, the ERG remains unconvinced that a WC-based economic model provides the most robust approach to assess the cost-effectiveness of ESA in MPS IVA patients.

Importantly, the thresholds for change in WC use defined by the company in the model are contradictory to the clinical outcome data observed at baseline in the MOR-001 and the MAA datasets. Given that change in WC use is the driver of the economic results, the ERG cannot support the use of the company's economic model to assess the relative costs and benefits of ESA. Nonetheless, and as a minimum requirement, if a model based on WC use was to be maintained, the thresholds for change in WC use would have to be revaluated and made consistent with the underlying clinical data.

The ERG considers that a model based around endurance and respiratory measures would have provided a better tool for decision making. Crucially, such modelling approach would have allowed the company to use the MAA or the MOR-005, and MOR-001 data to estimate the decrease (or increase) in 6MWT and FVC outcomes according to treatment arm, instead of relying almost solely on assumptions around disease progression.

Natural history of disease captured in the model

Clinical expert opinion provided to the ERG reflected that in clinical practice, MPS IVA patients do not use a wheelchair (95% of patients) or are asymptomatic (5%) at the point of initial diagnosis. This

is due to genetic contact tracing and evolving medical knowledge around the disease, which means that patients are diagnosed before needing a WC. Therefore, the ERG considers that the initial distribution of patients across the different WC states in the model does not reflect clinical practice, and requested that the company provided a scenario analysis where patients entering the model (i.e. starting treatment with elosulfase or best supportive care) were either in the asymptomatic stage [redacted] or in the NWC state ([redacted]%).

Finally, the ERG notes that the model structure does not accurately reflect the natural history of MPS IVA leading to the paraplegic state of the disease. In the model, patients could only enter the paraplegic state from the asymptomatic or the NWC states as a result of complications related to a cervical fusion operation. Furthermore, the company assumed that only asymptomatic and NWC patients would receive a cervical fusion operation. Clinical expert opinion provided to the ERG explained that both of these assumptions are inaccurate as: 1) most patients receiving cervical fusion surgery are on the NWC or the SWC states; and 2) that everyone can progress to the paraplegic state by natural progression of the disease (and by accident). Nonetheless, clinical expert opinion also reflected that most paraplegy cases are now avoided.

Therefore, even though the ERG considers that patients in all WC categories should have been able to transition to the paraplegic state, this issue pales in comparison with the other, more serious issues with the company's model structure.

With regards to patients receiving cervical fusion surgery, the ERG asked that the company included a scenario analysis in the model where only patients in the NWC and the SWC states received the surgery (and had the potential associated complications leading to paraplegy). Results are reported in Section 6.

4.2.5 Perspective, time horizon and discounting

A lifetime horizon of 100 years was adopted in the model and time was discretised into annual cycles (12 months) with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 1.5%. The use of a 1.5% discount rate was justified by the company by referring to the criteria specified in the NICE methods guide, where it is anticipated that the 1.5% discount rate is applicable to treating patients that would otherwise not survive; patients who suffer from severely impaired conditions or when a condition lasts for more than 30 years.

The ERG notes that the NICE Guide to the Methods of Technology Appraisal (2013) states that, "*In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years) […] A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved*."

The ERG is not certain that the use of a 1.5% discount rate is appropriate in this case, as the long-term benefits with ESA remain uncertain, particularly its impact on patients' survival (please see Section 4.2.6).

The ERG also disagrees with the company's approach to discounting costs and benefits in the first cycle of the model (cycle 0). The company did not use the proportion of patients at cycle 0 in the model, but instead started discounting outcomes only in cycle 1. The first discounting factor in cycle 1 of the model (1.5%) was applied to the proportion of patients estimated with the half correction between cycle 0 and cycle 1. As a result, and in order to estimate undiscounted outcomes in the economic analysis, the company multiplied the cycle 1 outcome (costs, QALYs or life years) by 2, in order to obtain the undiscounted outcome.

The ERG recommends that the company includes cycle 0 outcomes throughout the model, without a half-cycle correction, and with a discount rate of 1 (so no discount should be used in cycle 0). Year 1 in the model (cycle 1) should include the half correction from cycle 0 to cycle 1, and outcomes should start being discounted in this cycle with a discount factor of 1.5% (or another discount rate assumed in the model). This approach eliminates the need to multiply undiscounted outcomes by 2 in the first cycle of the model, which should be removed.

4.2.6 Treatment effectiveness

The transparency and clarity around data implementation in the model is very poor in the CS. Furthermore, references to data used in the model are unclear and incorrect in several instances. In several occasions during clarification, the company did not address the ERG's questions and instead sent repeated and vast quantities of information already contained in the CS. In combination, these issues made the ERG's review process extremely challenging.

Overall, the ERG found contradictory statements in the CS and remains unclear on the company's proposition around the value of ESA on improving patient outcomes.

As mentioned at the beginning of Section 4, the ERG also concluded that data used in the economic analysis to estimate the relative treatment effectiveness of ESA against SoC is unfit for decision making. Therefore, in this section, the ERG provides the following:

1. A description of the company's methods and assumptions used to estimate treatment effectiveness in the model;
2. A critique of the methods and assumptions made by the company where possible, and/or a list of further validation needed once the clinical data used in the model has been re-analysed by the company;
3. A list of recommended exploratory analysis to be conducted once the clinical data has been re-analysed.

As discussed in Section 3.8, the ERG concluded that the most robust set of data available to estimate the relative treatment effect of ESA compared to SoC is likely to consist of a complete case analysis using the full ITT population of MOR-005 QW-QW and the patients from Mor-CAP1. This should be followed by an assessment of the feasibility of a subsequent propensity score matching analyses for each outcome. Therefore, in this section, the ERG focused its recommendations around these two data sets.

4.2.6.1 Use of data to estimate treatment effectiveness in the model

Treatment effectiveness in the base case model was captured through the following clinical outcomes: WC use; 6MWT and FVC measures; surgeries; and mortality, which are discussed in turn in this section. To aid the discussion, the ERG has produced Table 31 to summarise how the different measures of treatment effectiveness were used in the economic model.

Table 31. Treatment effectiveness measures in company's base case

Treatment	Outcomes	Baseline distribution	Progression from baseline (1st year)	Progression from state at the end of year 1 (and following years)
Standard of care	Mean 6MWT (minutes)	NWC: 289 SWC: 180 WCD: 31 source: MOR-001	Outcome not used	Outcome used to determine progression from the NWC and SWC states (see below)
	Mean FVC (litres)	NWC: 1.34 SWC: 1.15 WCD: 1.03	Outcome not used	Outcome used to determine progression from the WCD and

		source: MOR-001		paraplegic states (see below)
	WC use:	source: ERT-naïve MAA and MOR-001	-	-
	asymptomatic	5%	3 years for patients to progress – assumption	
	NWC	40%	Table 77 CS	6.84m lost every year in the 6MWT – Harmartz 2013
	SWC	50%	Table 77 CS	6.84m lost every year in the 6MWT – Harmartz 2013
	WCD	5%	Table 77 CS	0.1L lost every year in FVC – assumption; and patients reaching 0.3L FVC move to the end-of life state
	Paraplegic	0%	In the first year of the model 10% of patients having a cervical fusion surgery enter the paraplegic state	0.1L lost every year in FVC – assumption; and patients reaching 0.3L FVC move to the end-of life state
	Survival	-	2.38 times greater than the general population mortality matched for age and gender	2.38 times greater than the general population mortality matched for age and gender
Elosulfase alfa	Mean 6MWT (minutes)	Outcome not used	Outcome not used	Outcome not used
	Mean FVC (litres)	Outcome not used	Outcome not used	Outcome not used
	WC use:	Same as SoC arm	-	-
	asymptomatic	Same as SoC arm	8 years for patients to progress – assumption	
	NWC	Same as SoC arm	Table 77 CS	[redacted] years to progress to the next WC state - assumption
	SWC	Same as SoC arm	Table 77 CS	[redacted] years to progress to the next WC state - assumption

	WCD	Same as SoC arm	Table 77 CS	[redacted] years to progress to the next WC state – assumption
	Paraplegic	Same as SoC arm	In the first year of the model 10% of patients having a cervical fusion surgery enter the paraplegic state	[redacted] years to progress to the next WC state – assumption
	Survival	-	Same as general population matched for age and gender	Same as general population matched for age and gender
Abbreviations: NWC: no wheelchair; SWC: sometimes wheelchair; WCD: wheelchair dependent; SoC standard of care				

4.2.6.2 Wheelchair use

Asymptomatic state

Patients starting the model in the asymptomatic state were assumed to have an annual probability of progression to the NWC (also considered the "symptomatic" state) of [redacted]% in the SoC arm. This estimate was based on the assumption that SoC patients take 3 years to become symptomatic. The company based this assumption on the Montaño *et al*. study.[3]

Asymptomatic patients on ESA were assumed not to progress in the first year of the model, and to have a probability of progression of [redacted] in the subsequent years. This estimate was based on the company's clinical experts' opinion that it would take patients on ESA an additional 5 years (so a total of 8 years) to become symptomatic, compared to SoC patients.

ERG critique

The ERG notes that the Montaño *et al*. study reported that the mean age of onset of disease was 2.1 years, with initial symptoms recognised between 1 and 3 years.[3] Therefore, the ERG recommends a scenario analysis where it is assumed SoC patients take 2 years to become symptomatic.

The ERG is unclear why patients on ESA were assumed not to progress from the asymptomatic state during the first year of the model. This means that the company's assumption of a 5-year delay on patients becoming symptomatic is actually a 6-year delay when compared to SoC patients. More importantly, this delay in patients becoming symptomatic was based on clinical expert opinion and

according to the ERG's clinical experts, even though a delay in the onset of symptoms could be possible, there is no evidence to suggest that such delay would translate into 5 or 6 years. Therefore, the ERG has requested that the company conducted a scenario analysis where this delay associated with ESA was removed from the model, and recommends this analysis is repeated once the clinical effectiveness data have been re-analysed.

NWC; SWC and WCD states

Patients' transitions from baseline NWC, SWC, and WCD states during the first year of the model were estimated from the entire population (as confirmed by the company in their response to clarification question B15) in the MOR-001 study and the ERT-naïve population in the MAA dataset (Table 77 in CS). The data used were based on the shift in WC use from baseline to 2 years in MOR-001 and 72 weeks in the MAA.

In the model's following years, SoC patients' progression was measured through changes in 6MWT from the NWC and the SWC states, and through changes in mean FVC from the WCD and paraplegic states – patients in the NWC and the SWC states were assumed to lose 6.84m in their 6MWT annually,[57] and once they reached the threshold of 207m (while in the NWC state) they would transition to the SWC. Once SWC patients reached the threshold of 46m they would move to the WCD state. Patients in the WCD and paraplegic states were assumed to lose 0.1L in FVC every year, and once they reached 0.3L FVC in the model they move to the end-of life state.

In the ESA arm, all patients were assumed to have an "improved WC status" after year 1 in the model. The company looked at the change in WC use data for the ERT-naïve patients in the MAA (as ex-trial patients did not have WC baseline use data in the respective trials) to categorise patients' disease course in the long term. The company used the results shown in Figure 8 to justify that the change in WC status in the MAA sustained the long-term "improved WC status" assumption of treated patients versus untreated patients.

The "improved WC status" in the model meant that the annual probability of patients remaining in the same WC state they were in at the end of year 1 in the ESA arm was [redacted]%. This means that in the ESA arm, there was a probability of [redacted]% of patients progressing to the next (more dependent) WC state in the model for the remaining of their lifetime. Mathematically, this assumption is the equivalent of assuming that it would take an ESA patient [redacted] years to progress on their WC dependency.

The company conducted two scenario analyses where the proportion of "improved WC status" patients decreased from [redacted] to [redacted] and [redacted]%.

Figure 8. Change in wheelchair status in MAA and MOR-001 populations

ERG critique

The ERG considers that the company's estimation of transition probabilities between the WC states is unfit for decision making.

Year 1 in the model

Method used by the company for obtaining WC use data

For the purpose of analysing WC data from the MOR-001 and MAA sources, the company defined WC use based on patients' answers to question 33 and question 33a on the MPS HAQ questionnaire as follows:

- Q33, if response is no (0) to this question – no WC use;
- Q33a, if response is the first 3 options (1,2,3) – sometimes WC use;
- Q33a, if response is 4th option (always) – WC dependent.

Despite the ERG's efforts to find the MPS HAQ questionnaire online, the latter could not be found. The clinical study report (CSR) to the MOR-005 study reported that the questionnaire is available in its Appendix 16.1.1. However, the company did not make this appendix available in the CSR documents sent to the ERG.

Therefore, the ERG remains concerned that WC use data collected from the ESA and comparator studies might not be consistent or comparable as neither of these publications nor associated documents explain how WC use data were collected. Furthermore, the MOR-001 publications do not report change in WC use over time, therefore, the ERG is unsure how the company obtained these data.

The ITT results provided by the company on 15 February contained WC use data for MOR-001 and the MAA. The WC use data collected in MOR-001 distributed patients in 4 possible categories on the use of walking aids: none; crutches; cane/walking stick; and walker/walking frame. Therefore, the MOR-001 IPD did not capture the same WC categories as those used in the company's model and captured in the MAA and MOR-005, and crucially, does not seem to include the WCD category.

However, the IPD data provided in the company's model in tab "FVC MorCAP Calcs" presents patients' FVC outcomes by WC state for MOR-001, where 13% of patients were classified at baseline as being WC-dependent.

Given that the patients identification (ID) number was included in both datasets, the ERG investigated some patients' individual clinical history to try to understand how data for the WCD state had been captured from the IPD.

The ERG is extremely concerned about the discrepancies found in its investigation. For example, patient [redacted] in the model, was classified as being WCD at baseline. However, the same ID patient in the company's IPD, had a missing answer for the walking aid question at baseline and crucially, had a 6MWT result of 160m at baseline, and a 6MWT of 123m at year 1, when the patient reported not needing any type of walking aid. This inconsistency was found for several patients in the IPD and in the model data, where for example, patients were classified as being WCD in the model and as only requiring a walker/walking frame in the IPD. Therefore, the ERG recommends that the company explains: 1) the discrepancies between the IPD and the data included in the economic model for WC use; 2) how the WC data was captured in MOR-001, especially for the WCD state; and 3) how the WC data captured in MOR-001 was allocated to the same WC categories included in the MAA and in the model.

Methods used by the company to analyse WC use data

The ERG disagrees with the company's method for estimating transition probabilities. Given the availability of annual WC use data, it is unclear to the ERG why the data used to model transitions in the first year of the model were taken as the WC change from baseline to 72 weeks in the MAA dataset and from baseline to 2 years in the MOR-001 study, respectively.

Therefore, the ERG recommends that the WC data used in the first year of the model is the annual probability of patients going from their baseline WC state to the Year 1 WC state, in both MorCAP1 and MOR-005 (using a complete case analysis approach). The ERG's preferred approach to selecting which patients' observations are to be included in the Year 1 period of analysis is discussed in Section 3.8.

The ERG recommends that a comparison of the first year of transition probabilities available from MorCAP1, and MOR-005 is conducted once the clinical data have been re-analysed. The ERG's preliminary comparison of the 2 datasets suggested that at the end of Year 1, the MOR-005 data revealed a pattern where ESA does not show a benefit compared with SoC patients in the NWC categories.

Years 2 and 3 in the model

The ERG requests that once the MoRCAP1 data have been re-analysed, and more details have been provided on the data analysis of WC used in MoRCAP1, the company:

1. Uses the WC annual data (year 1 to year 2; and year 2 to year 3, if possible) available from MorCAP1 to estimate transition probabilities between the NWC; SWC; and WCD states in the model for the first 2 or 3 years;
2. Provides the annual data referred in point 1.

Similarly, the ERG recommends that, once the MOR-005 data have been re-analysed, the company:

1. Uses the WC annual data (year 1 to year 2; and year 2 to year 3, if possible) available from MOR-005 to estimate transition probabilities between the NWC; SWC; and WCD states in the model for the first 2 or 3 years;
2. Provides the annual data referred in point 1.

Following years

The ERG has several concerns around the estimates used to derive the increase in WC dependency for SoC patients in the following years of the model, through the use of 6MWT and FVC outcomes. The company used the 6.84m decrease in 6MWT reported in Harmatz *et al*. to estimate patients' increase in WC use in the NWC and the SWC states. Even though the company reported that the ITT population from the study was used, the estimate taken was that of the matched population to the MOR-005 study. The annual decrease seen in the ITT population in the study was 4.86m (instead of 6.84). [57] The ERG, therefore, recommends that:

1. The value used to estimate the change in 6MWT outcomes for SoC patients is taken from the re-analysis of the MorCAP1 IPD according to the recommrendations in Section 3.8;
2. The value used is based on the available annual estimate (similar to what has been requested for changes in WC use).

Additionally, the company chose not to take the change in FVC measures from the Harmatz *et al*. 2013 study and instead assumed an annual 0.1L decline based on clinical expert opinion. The Harmatz *et al*. study reported an increase in patients' FVC over the period of the study of 2.44% in total FVC (L) per year (ITT population) and of 2.39% for the MOR-005 matched population.

The company did not provide a justification for using the 6MWT decline for SoC patients from the Harmatz *et al*. 2013, while ignoring the increase in FVC for the same patients in the study. Without a robust clinical justification for the company's decision, the ERG does not agree the company's approach as it is biased in favour of ESA. The ERG, therefore, recommends that:

1. The value used to estimate the change in FVC outcomes for SoC patients is taken from the re-analysis of the MorCAP1 IPD according to the recommendations in Section 3.8;
2. The value used is based on the available annual estimate (similar to what has been requested for changes in WC use).

The ERG disagrees with the company's assumption that after Year 1 in the model, only [redacted] of ESA patients progress to the next (more dependent) WC state in the model, per year. The ERG's preliminary investigation of the MAA and MOR-005 data did not substantiate this assumption, and has shown that for ESA patients, WC dependency could still worsen, stabilise, or improve at Year 3, therefore, contradicting the company's assumption that ESA patients have a stable WC use from

Year 1 until they die in the model. The ERG caveats this analysis with the fact that the data used are not based on the complete case analysis of these studies, and so recommends that:

1. The value used to estimate the change in 6MWT outcomes for ESA patients is taken from the re-analysis of the MOR-005 data according to the recommendations in Section 3.8;
2. The value used is based on the available annual estimate (similar to what has been requested for changes in WC use);
3. The value used to estimate the change in FVC outcomes for ESA patients is taken from the re-analysis of the MOR-005 according to the recommendations in Section 3.8;
4. The value used is based on the available annual estimate (similar to what has been requested for changes in WC use);
5. The company ensures that any long-term assumptions of treatment effectiveness made in the model are consistent with the underlying clinical data for WC use.

The assumption that [redacted] of ESA patients do not have disease progression in the model seems to be the key driver of the company's base case economic results. For example, if all ESA patients in the model were assumed to be mild progressers instead of stable patients, which in the model meant that ESA patients would progress [redacted] less than SoC patients (but still had some progression) the company's base case ICER would increase from [redacted] to [redacted]. The ERG reinforces that this ICER still includes an assumption of ESA being twice as effective as SoC in delaying patients' progression to the next, more dependent, WC state.

Furthermore, the ERG's preliminary analysis of the MOR-005 data and the MAA data suggest a pattern where ESA does not show a benefit compared with SoC patients in the NWC categories. The ERG recommends that once the MOR-005 and the MorCAP1 data have been re-analysed, the company conducts a comparison of the annual values for 6MWT and FVC outcomes in both studies and assesses if additional scenario analysis should be conducted. For example, if the data indicates that ESA might not have a benefit against SoC for NWC patients, the ERG recommends including an option in the model where ESA does not have a benefit against SoC for NWC patients.

Finally, and as discussed in Section 4.2.4.1, in case the company decides to maintain the model structure to be focused around WC use, the thresholds for change in WC use should be revaluated and made consistent with the underlying clinical data in MorCAP1 and MOR-005.

The exit thresholds used by the company of 207m to exit the NWC state and of 46m to exit the SWC state are claimed to have been taken from the same Harmatz *et al*. 2013 study. Nonetheless, the ERG could not find these estimates anywhere in the publication. The [redacted]L threshold used to exit the WCD and paraplegic states was based on the company's clinical experts' opinion.

Paraplegic and end-stage states

During the first year of the model, patients could transition from the asymptomatic or NWC states to the paraplegic state as a result of unsuccessful cervical fusion surgery. In the following years, patients could progress from the WCD and the paraplegic states into the end-stage state, where patients were assumed to always be in a WC and require continual mechanical ventilation as their FVC threshold reached [redacted]L or less.

SoC patients progressed from the WCD and the paraplegic states into the end-stage state through changes in mean FVC. An assumed change of 0.1L per year meant that SoC patients take 7 years to reach the [redacted]L threshold.

Patients on ESA were assumed to have an annual probability of [redacted] of remaining in the WCD and in the paraplegic states.

Once patients entered the end-stage disease they were assumed to remain there for 2 years before dying.

ERG critique

The clinical experts advising the ERG noted that for children, mechanical ventilation is not frequently used as children who develop tracheal obstruction are usually managed with some form of non-invasive oxygen and medication. For adults, mechanical ventilation is more common; however, the clinical experts said this would not be 24-hour mechanical ventilation. The experts added that while the 2-years assumption in the end of stage disease state is not unreasonable, patients would more commonly stay in this state for 1 year before dying.

The ERG found an error in the economic model as patients in the NWC (or SWC) state were being given a probability of cervical fusion of 0% instead of the 38% intended by the company (for example, please see cell BS14 in "PF_comparator_Sym" tab, where the "p_FusionOP_Sometimes" needs to be replaced with "p_FusionOP_never" in the formula).

Therefore, the ERG recommends that the company corrects the error in the model.

4.2.6.3 Mortality

In the company's base case analysis, mortality for patients treated with ESA was assumed to be the same as that of the general population matched for age and gender.

The relative risk (RR) of mortality for SoC patients was assumed to be 2.38 greater than the general population mortality (and therefore, the mortality estimated for ESA patients). The company based its assumption on Quartel *el al*. 2018, a 15-year study of MPS VI patients treated with galsulfase. The study showed that 24% of patients treated with galsulfase had died after 15 years of treatment, while 57% of treatment-naïve patients had died over the same period. The company used these data to estimate the RR of death as 2.38 (57%/24%) and applied it to the ESA patients' mortality to estimate mortality for SoC patients.

The company also reported that the assumption of similar survival benefit across ERT treatments in different MPS disorders is based on the assumption of similar mechanisms of improvement in pulmonary function.

As a scenario analysis, the company estimated mortality as consequence of decreased %FVC in the model. The ERG notes that in the company's updated model, provided post-clarification, this scenario was not working; therefore, the ERG recommends that the company corrects this in the model so the scenario can be run.

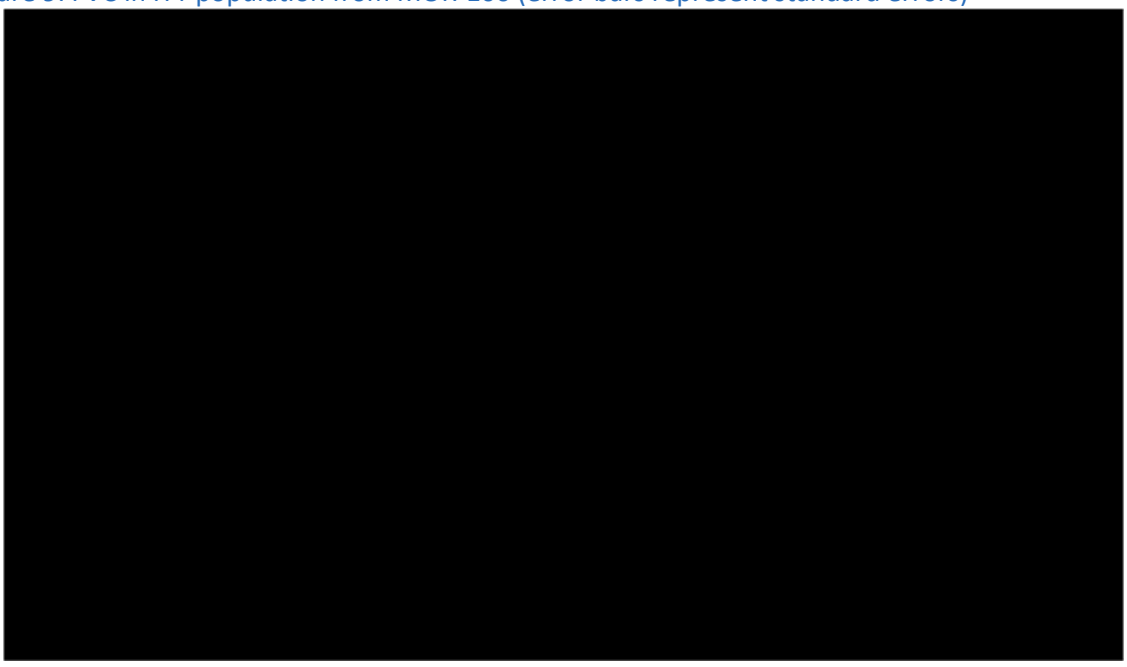
Average baseline values of %FVC were assigned to the different WC states in the comparator arm of the model based on the mean absolute baseline values in. The % FVC values were obtained for each patient by dividing the absolute FVC values at baseline by the predicted FVC value. The company reported that the predicted FVC values were calculated according to the recommendations by the European Respiratory Society and by using the reference equation of European Community for Steel and Coal (Quanjer *et al.* 1993):

- For males: (5.76*height) - (0.026*age) – 4.34
- For females: (4.43*height) - (0.026*age) – 2.89

Given that MOR-001 did not include asymptomatic or end-stage patients, the company used clinical expert opinion to determine baseline %FVC for these patients.

To estimate the impact of ESA on %FVC (and thus, on mortality) the company used an improvement factor of %FVC vs baseline of [redacted] over the course of 3 years of treatment with ESA. The company reported the source of the improvement factor to be the MOR-002/100 trial, more specifically the data taken from Figure 9, where the percent change in FVC for the MOR-002 population was captured over 72 weeks, followed by an additional 72 weeks of percent change in FVC data in the extension study MOR-100.

Figure 9. FVC in ITT population from MOR-100 (error bars represent standard errors)



By applying the 16.5% improvement on SoC %FVC values, the company estimated the %FVC values for ESA. Finally, the company assumed that for every 10% decrement in FVC compared to 100% predicted FVC there was a RR for mortality of 1.12.[64] The company then applied the resulting RR to the general population mortality to estimate deaths per health state, per treatment arm. The mean %FVC values, decrements and RR estimated for each health state in the model are reported in Table 32.

Table 32. Decrease in %FVC and mortality risk per WC state, per treatment arm

Wheelchair state	Predicted FVC		Resulting relative risk for mortality (based on 1.12 per 10% decrement)
	Baseline	Decrement from 100%	
Standard of care arm			
Asymptomatic	80%	20%	1.25

No wheelchair use	25%	75%	2.34
Sometimes use wheelchair	23%	77%	2.39
Wheelchair dependent	18%	82%	2.53
Paraplegic	18%	82%	2.53
End-stage	10%	90%	2.77
Elosulfase alpha arm			
Asymptomatic	80%^	20%	1.25
No wheelchair use	43%*	57%	1.92
Sometimes use wheelchair	40%*	60%	1.98
Wheelchair dependent	31%*	69%	2.18
Paraplegic	31%*	69%	2.18
End-stage	10%^	90%	2.77
* these values were estimated by applying the 16.5% improvement on SoC %FVC baseline values ^ assumed the same as SoC			

4.2.6.4 ERG critique

Company's base case

The ERG has several issues with the company's estimation of mortality in the base case analysis, for both treatment arms.

Clinical expert opinion provided to the ERG informed that for a mild form of MPS IVA, patients treated with ESA could live to be around 50 or 60 years old. However, there are [redacted] of ESA patients alive at 93 years old in the model. This suggests a clinically implausible scenario and an overestimation of survival in the model.

The ERG's clinical experts also disagreed with the company's assumptions that ESA patients experience the same mortality as the general population matched for age and gender. This was considered clinically implausible as many of the complications of MPS IV that cause death are not normalised by ESA, such as cardiac valvular disease, cervical spinal compromise, chest deformities (which cause restrictive lung disease), and tracheal obstruction.

Furthermore, the ERG considers that the company has provided no evidence of the potential similarity across survival outcomes for the different MPS conditions with or without ERT treatments. Clinical expert opinion provided to the ERG also confirmed that outcomes for MPS VI cannot be assumed the same as those for MPS IVA.

Even if it could be shown that comparable outcomes are observed in MPS VI and MPS IVA, the company is underestimating the mortality observed in the Quartel *el al*. 2018 study. Their research in MPS VI patients treated with galsulfase, shows that the 5-year mortality rate for MPS VI ERT-treated patients was [redacted]%. This compares to [redacted]% estimated by the company for ESA patients in the model (matched for age). Furthermore, at the end of the 15-year follow up period in the Quartel *el al*. 2018 study, there were about 65% of ERT patients alive and 40% of SoC patients alive, while in the company's model there were [redacted]% of ESA patients alive after 15 years of treatment and [redacted]% alive in the SoC arm.

The ERG notes that if the company can substantiate that the same survival observed for MPS VI patients on ERT treatment and on SoC can be assumed for MPS IVA patients, then instead of using the RR observed in Quartel *el al*. 2018 and applying it to the general population mortality, the company should use the 15-year Kaplan-Meier survival data observed for ERT-treated and SoC patients in the same study in their analysis (as the company's approach clearly overestimates the survival observed for both treatment arms in Quartel *el al*. 2018).

Company's scenario analysis

As discussed in Section 4.2.4.1, linking FVC outcomes observed in the key data sources to mortality could have provided a valuable analysis. However, the company's scenario analysis makes little use of the change in FVC outcomes for ESA and SoC in their respective data sources.

Furthermore, the ERG has concerns with the methodology used in the company's scenario analysis. These consist of the following: 1) the improvement factor of [redacted]% used by the company; 2) the estimation of increased risk of mortality associated with decreased % FVC. These are discussed in turn below.

1. The improvement factor used by the company:

The ERG is unclear why the FVC improvement over time for ESA was taken from MOR-100, instead of the MAA data, used in other instances of the company's analysis. MOR-100 was an extension study

with patients from MOR-002, where all patients took part in dose escalation (ESA 0.1 mg/kg/QW for weeks 1-12, 1.0 mg/kg/QW for weeks 13-24 and 2.0 mg/kg/QW for weeks 25-36 and then 2.0 mg/kg/QW in MOR-100). The choice of MOR-100 was not justified by the company and introduces additional heterogeneity in the model population given the dose escalation regime and the difference in baseline population when compared to the MAA study.

Regardless, given the ERG's recommendation that MOR-005 is used instead of the MAA as a source of clinical effectiveness for ESA, the ERG recommends that the company analyses the improvement factor in FVC over time observed in MOR-005 to be applied in this scenario.

2. Estimations of increased risk of mortality as %FVC decreases:

The company assumed that for every 10% decrement in FVC compared to 100% predicted FVC there is a RR for mortality of 1.12. This estimate was reported to be taken from the Neas and Schwartz, 1988 study. However, the ERG believes that the right estimate intended to be used by the company was 1.15 and importantly, that the estimate is not a RR but instead a rate ratio (as reported in the study). The only reference to a rate ratio of 1.12 in the paper is in reference to the increase in mortality for a 10% decrement in the FEV/FVC ratio in the study. The estimate of the impact of a drop in FVC of 10% is given as rate ratio of 1.15 in the study.

Therefore, the company should have used the 1.15 value and instead of multiplying the estimate by the general population mortality (which would be appropriate if the company had a RR estimate), the company should have exponentiated the general population mortality to the 1.15 value for every cycle. Therefore, the ERG recommends that the company replaces the value used and the method for implementing it in the model.

Finally, the ERG notes that a scenario linking the change in FVC to mortality would be the ERG's preferred approach to estimate survival in the model, as the latter relies on fewer assumptions than the company's base case, and importantly, could link the underlying clinical FVC data used in the model to the estimation of mortality. It is important though, that the company ensures that the change in FVC data from M0R-001 and MOR-005 (once re-analysed according to the ERG's recommendations) are used to estimate mortality in the economic analysis.

4.2.6.5 Surgery

Patients in the asymptomatic; NWC; SWC; and WCD states could have surgery at the beginning of every year according to the probabilities in Table 33. The surgical events were not explicitly captured in the model, but instead the outcomes related to surgery (paraplegy or death) were estimated every cycle, according to Table 34. Patients could not have the same type of surgery more than once while in the same health state. The company assumed that after surgery patients entered a recovery period, during which they had reduced quality of life.

Table 33. Probability of surgery by wheelchair dependency state

Surgery	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent
Cervical Fusion Operation	37.5%	37.5%	0.0%	0.0%
Genu Valgum surgery	0.0%	0.0%	41.0%	0.0%
Spinal decompression surgery	0.0%	0.0%	40.0%	0.0%
Hip surgery	0.0%	0.0%	0.0%	6.8%
Lower spine surgery	0.0%	23.0%	0.0%	0.0%
Aortic valve replacement	0.0%	0.0%	0.0%	15.0%
Tonsillectomy	43.0%	0.0%	0.0%	0.0%
Ear tube placement	36.0%	0.0%	0.0%	0.0%
Corneal al replacement	3.4%	0.0%	0.0%	0.0%
Cataract surgery	3.4%	0.0%	0.0%	0.0%

Table 34. Surgical outcomes

Surgery	Successful	Paraplegic	Death
Cervical Fusion Operation	78%	10%	12.0%
Genu Valgum surgery	94%	0%	5.8%
Spinal decompression surgery	90%	0%	10.2%
Hip surgery	94%	0%	5.8%
Lower spine surgery	94%	0%	6.4%
Aortic valve replacement	84%	0%	16.0%

Tonsillectomy	98%	0%	2.3%
Ear tube placement	98%	0%	2.1%
Carpal Tunnel Surgery	98%	0%	2.1%
Corneal replacement	98%	0%	2.1%
Cataract surgery	78%	10%	12.0%

The company modelled the treatment effect of ESA on surgery through the following assumptions:

1. Treatment delays the need for all surgeries by 4 months;
2. Treatment with ESA leads to faster recovery after surgery.

When asked to justify the first assumption during the clarification stage, the company reported that the latter was based on MOR-004/005 data taken from Figure 10. The 4-month delay in surgery was reflected in a delay of incurring the surgery costs and the surgery-related disutilities in the ESA arm, by 4 months.

Figure 10. Time to surgery in MOR-004/MOR-005 in weeks (Figure 14.2.6 in CSR)

The second assumption was based on clinical expert opinion and the recovery period assumed for the different surgeries is given in Table 35, per treatment arm.

The disutilities related with surgery are covered in Section 4.2.8 of the ERG report.

Table 35. Duration and utility decrement of recovery period following surgery

Surgery	Utility Decrement	Recovery period (months)	
		Standard Care	Elosulfase + Standard care
Cervical fusion surgery	0.250	6	4
Genus Valgum			
Spinal decompression			
Hip surgery			
Lower spine surgery			
Aortic Valve replacement	0.010	6	4
Tonsillectomy	0.005	2	1
Ear Tube Placement			
Corneal Replacement			
Cataract Surgery			

4.2.6.6 ERG critique

Clinical expert opinion provided to the ERG reflected that the proportions of surgeries per WC use modelled by the company were not reflective of UK clinical practice. For example, the ERG's clinical experts disagreed with the assumption that 38% of asymptomatic patients would receive cervical fusion surgery. Other issues included hip surgery, which the ERG's clinical experts considered was more frequent and more common across all WC categories than the company had assumed, as was lower spine surgery; aortic valve replacement; tonsillectomy; and ear tube placements. The ERG's clinical experts mentioned that corneal replacements are extremely rare in the NHS and therefore suggested that these were removed from the analysis. The ERG's clinical experts' suggestions are reported in Table 36. At the request of the ERG, the company provided a scenario analysis using these estimates and concluded that the impact on the ICER was small.

Table 36. Probability of surgery according to ERG's clinical experts

Surgery	Asymptomatic	No wheelchair use	Sometimes use wheelchair	Wheelchair dependent

Cervical Fusion Operation	0%	37.5%	37.5%	0.0%
Genu Valgum surgery	0.0%	0.0%	41.0%	0.0%
Spinal decompression surgery	0.0%	0.0%	40.0%	0.0%
Hip surgery	0.0%	17.5%	17.5%	17.5%
Lower spine surgery	0.0%	23.0%	17.5%	0.0%
Aortic valve replacement	0.0%	15%	10%	15.0%
Tonsillectomy	43.0%	15%	0.0%	0.0%
Ear tube placement	36.0%	15%	0.0%	0.0%
Corneal al replacement	0%	0.0%	0.0%	0.0%
Cataract surgery	0%	0.0%	3.4%	3.4%

Once again, the ERG notes that the company's choice of model parameters lacks transparency. The ERG is unsure how a 4-month delay associated with ESA vs SoC was estimated by the company using Figure 10. The latter shows the cumulative incidence of surgery when all patients in MOR-005 were already receiving ESA, therefore there are no data in the figure for purely placebo patients, only patients who initiated ESA later. The ERG suspects the company might have used time to first surgical event in the QW-QW arm (approximately 52 weeks) minus time to first surgical event in the PBO-QW (approximately 36 weeks) to arrive at the 4 month (16 weeks) delay. The ERG cannot guarantee this was the case, however, notes that the latter would be considered a flawed approach. Therefore, the ERG recommends that the company: 1) explains how the 4-month delay was estimated and 2) conducts a scenario analysis where the assumption of surgery delay is removed from the model.

The faster recovery assumed for ESA patients after surgery was based on an assumption, on which the ERG's clinical experts did not reach a consensus. While one clinical expert thought it was reasonable that ESA patients could have a faster recovery due to improved general health, the other did not agree that ESA would lead to faster post-surgical improvement. Nonetheless, both experts mentioned that quantifying such a benefit would be extremely difficult. The ERG notes that the relative benefit is also different across surgeries, with ESA patients recovering from ear tube placement; corneal replacement and cataract surgery 1 month quicker that SoC patients; and with

ESA patients recovering 2 months quicker than SoC patients for all other surgeries. Therefore, the ERG recommends that the company conducts a scenario analysis to explore the impact of removing the assumption of faster recovery from the model.

The ERG reiterates its concerns with the assumptions made by the company on treatment effectiveness, and with the fact that these were poorly justified and substantiated in the economic analysis.

4.2.7 Adverse events

Treatment-related adverse events (AEs) are not explicitly included in the economic model as the company stated that the only relevant AEs associated with ESA incur during drug administration. Therefore, the company assumed that the costs associated with AEs were captured in the drug's administration costs, specifically in the use of prophylactic medication for side effects, and that these costs would be unlikely to have a significant impact on the cost-effectiveness results (section 12.2.4 of the CS). While the CS reported the costs of treating infusion-related AEs, these costs were ultimately not included in the model.

Surgical AEs were accounted for in the rates of surgical complications (tables 83 and 84 in the CS).

4.2.7.1 ERG Critique

The ERG's clinical experts disagreed with the company's assumption that the only relevant AEs related to ESA occur during treatment administration. The HST2 ERG report included AEs with rates sourced from MOR-004. Sixteen percent of patients experience at least one severe adverse event at 24 weeks and 24% at >48 weeks. The most common serious AEs were hypersensitivity, infusion-related reaction, anaphylactic reaction, bronchospasm and urticaria, of which anaphylactic reaction was the most serious. The HST2 ERG report also included rates of treatment discontinuation due to AEs of 22%. Discontinuation due to AEs, however, was not included in the company's current model.

At clarification the ERG queried the omission of AEs from the model. The company provided a narrative summary of the AE data from the most recent Periodic Benefit Risk Evaluation Report (PBRER) report submitted to the European Medicines Agency (EMA). In this report, [redacted] of patients taking ESA had an infusion-related adverse event, of which [redacted] were considered serious. There were [redacted] anaphylaxis incidents, of which [redacted] occurred within the first 24 hours after treatment. [redacted] required no treatment, [redacted] required antihistamines and the remainder ([redacted])

were treated with epinephrine and other supportive therapies. The company does not state whether any of these patients required hospitalisation.

Other infusion reactions were common, with [redacted]). The company breaks these down as [redacted] events occurring within the first day, and [redacted] of these being classified as serious (approximately [redacted] of all infusion reactions, including anaphylaxis).

Therefore, the ERG disagrees with the company's assumption that adverse reactions to treatment would be covered entirely by the premedication regimen and the administration costs (see section 4.2.9), especially as [redacted] (see section 4.2.9), and a big proportion of the events are likely to occur within 24 hours, not just during the [redacted].

Nonetheless, it is unlikely that the impact of including treatment-related AEs in the model would have a significant impact on the ICER. In the latest safety data, the most severe AEs are anaphylaxis which was treated with an inexpensive medication and is unlikely to have a lasting impact on patients' quality of life.

4.2.8 Health-related quality of life

Health related quality of life (HRQoL) was captured with the EQ-5D-5L for patients in the MAA. The MOR-trials did not collect EQ-5D data but instead used the MPS-HAQ disease-specific quality of life measure. Therefore, the company used the baseline EQ-5D-5L utility values captured in the MAA for ERT-naïve patients to estimate quality of life for SoC patients and used the utility values form the last follow-up assessment for the same patients to estimate quality of life for ESA. These data were used to estimate the utility associated with the NWC; SWC; and WCD states. Asymptomatic patients were assumed to have a utility value of 1. Paraplegic and end-stage patients were assumed to have the same utility values as those used in the HST2, which correspond to 0.057 for paraplegic patients; and 0.024 for the end-stage health state.

The company also applied a treatment specific utility increment to the health states in the ESA arm of the model. The company's justification was that EQ-5D-5L is not sensitive enough to capture the increase in 6MWT and in FVC outcomes for the ESA arm. Even though this information was not provided in the CS, the model included the company's estimate for the mean gain in 6MWT in the

ESA arm (60m) and increase in mean FVC (0.054L) to derive the utility increment. The estimation of the 60m and 0.054L gain associated with ESA is discussed in the next subsection.

The increment was calculated using regression data reported in Lampe *et al.* 2015, which showed a 0.002 QALY gain for a 1m increase in 6MWT and 0.2 QALY gain for 100m gain; and a 0.2 QALY gain for a 1L increase in FVC for adult patients. Therefore, for the 60m gain in 6MTW assumed for ESA patients, the company estimated a utility increment of [redacted] and of [redacted] associated with the gain of 0.054L in FVC.

The 0.12 additional QALY gain was added to the NWC and SWC health states, and the 0.01 increase was added to WCD and the paraplegic states in the ESA arm.

A full list of the utility values used in the SoC arm, the treatment specific increments, and the utility values used in the ESA arm in the company's base case are show in Table 37.

Table 37. Model utility values

Health state	Utility value at baseline in MAA dataset, ERT-naïve patients and used in SoC arm (SE)	Last follow up value in MAA dataset, ERT-naïve patients (SE)	Change	Treatment specific increment	Utility value used in ESA arm (SE)
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SE, standard error; Soc, standard of care; ESA, elosulfase alpha

4.2.8.1 ERG critique

Given that the company's analysis of EQ-5D data from the MAA is likely to have been done through the same method as the other clinical outcomes in the MAA, the ERG recommends that the

company re-analyses the MAA EQ-5D data with the complete case analysis method, before further inferences can be made on the changes in QoL for MAA patients.

The ERG also found discrepancies in the mean utility values provided by the company in their clarification response to question B19, and the company's IPD on patients' quality of life. The ERG's preliminary analysis of the IPD revealed differences in the number of patients and crucially, considerable differences in mean utility values per WC state. Without understanding why the values in the company's IPD and in the company's results differ, the ERG cannot recommend these data are used in the economic analysis.

Additionally, the ERG does not agree with the assumptions that underpin the health state utility values used in the model.

The company reported that based on the long-term MAA ex-trial data, patients' quality of life remains stable for 10 years, therefore point estimates from baseline and end of follow-up periods could be used to estimate the utility associated with the SoC and ESA arms, respectively. The ERG's preliminary analysis of the QoL data from the MAA did not corroborate the company's assumption. Given that the company's analysis of QoL from the MAA is likely to have been done through the same method as other clinical outcomes in the MAA, the ERG recommends that the company re-analyses the MAA EQ-5D data with the complete case analysis method.

The ERG notes that the company's justification for having treatment-specific utility values by WC category is inconsistent with the company's justification for having a WC based model. If, as the company suggests, WC use is the most appropriate measure for capturing the change in patients' quality of life, then the impact of ESA on patients' WC change should be enough the capture the change in patients' quality of life.

Furthermore, using different utility values per treatment arm in the same WC state, combined with the utility increments estimated for FVC and 6MWT gains in the ESA arm, double counts the benefits associated with the ESA in the analysis. Given the ERG's view that the WC categories used by the company are not appropriate to capture the benefit of ESA (see Section 4.2.4), the ERG's preference is to assume that all WC states have the same utility in the model, and apply utility increments associated with gains in the 6MWT and FVC outcomes observed for ESA.

The ERG requested a scenario analysis where the utility estimates from the original company submission for the HST2 were used (which in turn where taken from the Hendriksz *et al*. 2014[63] burden of disease study for patients with MPS IVA). These were 0.846; 0.582; and 0.057 respectively, in adults not using a wheelchair, using a wheelchair only when needed, and always using a wheelchair. In the scenario analysis requested by the ERG, the utility values for the asymptomatic, paraplegic and end of stage patients were to remain the same (as they were taken from the CS for HST2).

The ERG remains unclear as to how the company estimated the mean gain in 6MWT in the ESA arm (60m) and increase in mean FVC (0.054L) to derive utility increments. If the company decides to use these gains in their updated base case analysis, the ERG recommends that a clear explanation of the sources used, and the calculations and assumptions undertaken are provided.

Nonetheless, the ERG's preferred option for modelling utility in the model corresponds to a scenario where the utility increments associated with ESA are estimated by using the FVC and 6MWT results underpinning the treatment effectiveness analysis and the clinical data used in the model.

Given the likely uncertainty around the FVC and 6MWT benefits associated with ESA resulting from the comparison of MorCAP1 and MOR-005 data, the ERG also recommends an exploratory analysis where no utility increments are assumed for ESA. In this scenario, patients' gain in quality of life comes from changes in WC use, and the movement across these states in both treatment arms.

Burden on carers' quality of life

The company's base case included the costs and QALY decrements for carers of patients. The utility values associated with caring time were derived from studies focused on carers of patients with multiple sclerosis. The company used values from Gani *et al.* 2008[65] in their base case analysis and used values from Acaster *et al.* 2013 [66] as an alternative source in the model, although this was not reported in the CS.

The Gani *et al*. 2008 study estimated disutilities according to expanded disability status scale (EDSS) health states (in patients who had Alzheimer's disease as well as multiple sclerosis) and according to the amount of caregiver time required for patients in each health state. The hours of caregiving assumed in the company's analysis were taken from Hendriksz *et al*. 2014.[63] The utility values, hours of care and EDSS score are presented in Table 38.

Table 38. Carer utility mapping (adapted from table C31 in HST2 submission and page 292 of the CS)

Wheelchair health state	Average hours of care (reported in HST2)	EDSS score	Utility value
Asymptomatic	0.0	0-3	0
No use Wheelchair	0.0	0-3	0
Sometimes use wheelchair	2.4	4.5-5.0	-0.02
Wheelchair dependent	11.3	7.5-8.0	-0.11
Paraplegic	14.8	8.5-9.5	-0.14
Predeath	14.8	8.5-9.5	-0.14

Abbreviations: EDSS, Expanded Disability Status Scale;

Acaster *et al.* 2013 included 200 caregivers of multiple sclerosis patients with reported EQ-5D scores. The study used the patient determined disease steps scale (PDDS) to assess mobility in multiple sclerosis patients. PDDS ranges from 0 (normal) to 8 (bedridden). In their scenario analysis, the company mapped these to the health states used in the model, as reported in Table 39.

Table 39. Acaster *et al.* 2013 mapping

Wheelchair health state	PDDS score	Utility value
Asymptomatic	0 (normal)	0
No use Wheelchair	0 (normal)	0
Sometimes use wheelchair	7 (bilateral support)	-0.142
Wheelchair dependent	7 (bilateral support)	-0.142
Paraplegic	7 (bilateral support)	-0.142
Predeath	8 (bedridden)	-0.095

ERG critique

The estimation of carer disutilities was not well explained in the CS. Nonetheless, the use of Gani *et al*. 2008 values has been previously accepted by the HST2 committee.

The ERG notes that the company's alternative values incorporated in the model from Acaster *et al.* 2013 had an error in the model, as the pre-death state utility value was applied as a utility gain rather than a disutility. As these values were not used in the base case analysis, this error does not impact the results.

4.2.8.2 Adverse event disutilities

Adverse event disutilities were only included for surgeries and were assumed to last for one cycle in the model (one year). The company used an expert elicitation Delphi process to estimate three disutility values, one for minor surgery (0.05); one for aortic valve replacement (0.10); and one for major surgery (0.25) – see Table 86 in the CS for more detail. The company assumed that ESA patients would recover from surgery quicker, but that everyone receiving the surgery would experience the same AE disutilities.

ERG critique

The ERG notes that the most appropriate method to find disutility data is to conduct a systematic literature review and completement or validate the latter with clinical expert opinion. However, the company's response to question B23 explained that a literature search was not conducted, and only expert opinion was sought to derive disutilities.

Nonetheless, the ERG ran a scenario analysis exploring the use of different disutilities associated with surgery and concluded that these do not have a significant impact on the ICER.

4.2.9 Resource use and costs

The company included the following costs in the economic model: drug acquisition costs; administration costs; surgical costs; adverse event costs; carer costs; and resource use costs. The details for each of these are given in the following subsections.

Unit costs used in the model were inflated to 2018/2019 prices using the PSSRU hospital and community health services pay and prices index.

4.2.9.1 Drug acquisition costs

Elosulfase alfa is an intravenous drug administered weekly over four hours at a dose of 2mg per kilo of body weight. The list price per 5mg vial is £750. In the model, the average weight for patients in

each health state was derived from the MAA population and used to calculate the ESA dose administered. The average weight, vial use and cost for each health state in the model is detailed in

Table 40. The number of vials was rounded up to the nearest whole number, to account for drug wastage.

Information on relative dose intensity was not given by the company in their submission and therefore patients in the model were assumed to receive the full prescribed dose of ESA in every cycle.

The comparator, SoC, has no drug acquisition costs.

Table 40. Dosing of elosulfase alfa by health state

Health state	Average weight (KG)	Vials	Weekly cost
Asymptomatic	12.30	5.00	£3,750
No use wheelchair	21.36	9.00	£6,750
Some use wheelchair	22.20	9.00	£6,750
Wheelchair dependent	44.90	18.00	£13,500

Abbreviations: KG, kilogram

ERG critique

Impact of weight on costs according to company's IPD data

During clarification, the ERG enquired about the impact of patients' weight on the model results, as the cost of treatment per cycle will increase by £750 for every 2.5kg of body weight and the weight range observed in MAA patients was quite broad (10 to 68.4kg). The ERG also enquired about patients' change of weight over time as some patients started the model before being fully developed.

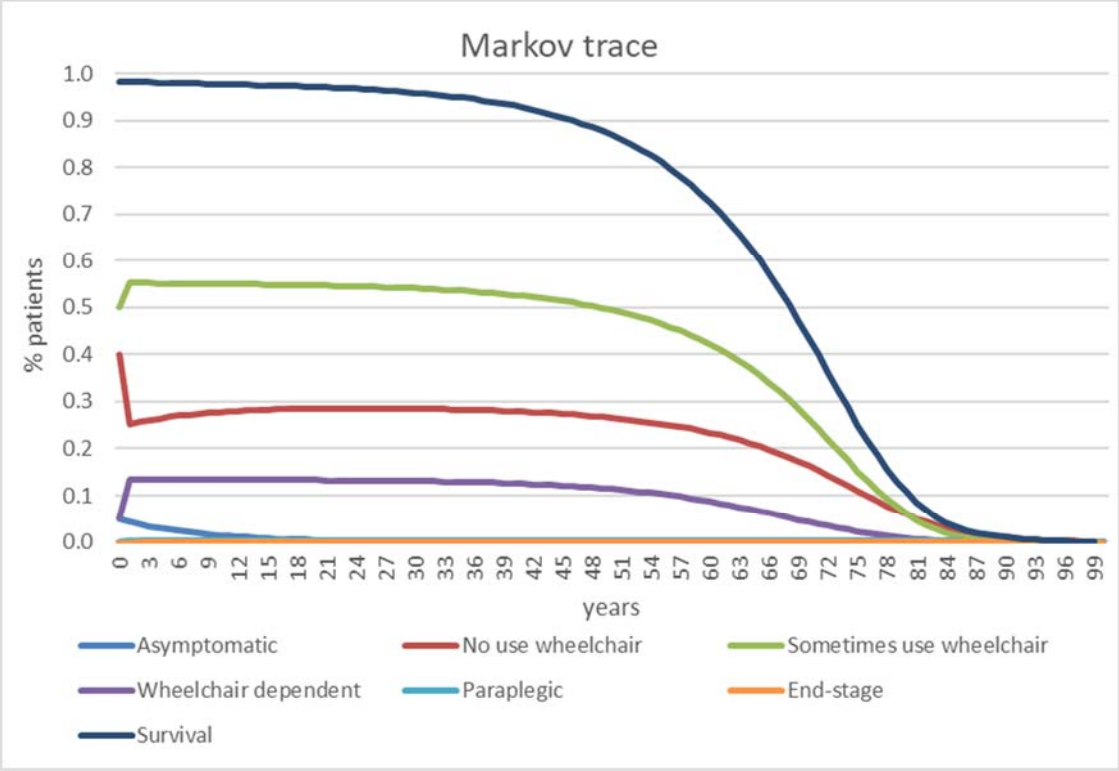
The company provided the ERG with IPD data and explained that weight categories did not need to be taken into consideration as the average number of vials ([redacted]) needed in the MAA population was the same whether it was based on the average weight of the population or the individual patient weight.

The ERG's preliminary investigation of the IPD concluded that the company underestimated the cost of ESA in the model. The IPD shows that the average number of vials used in the MAA was indeed [redacted] or ([redacted] if vial wastage is accounted); however, this estimate does not correspond to the average number of vials modelled by the company. As the company used the average weight of patients in each WC state (

Table 40) and patients were not evenly distributed across the WC categories at baseline (5% asymptomatic; 40% NWC; 50% SWC; and 5% WCD), the weighted average of patients' weight at the beginning of the model was actually 25.2kg, which corresponds to an average of 9.04 vials per week (and 470 vials per model cycle). These values compare to the MAA IPD average weight of [redacted] kg and [redacted] average number of vials per week, and [redacted] vials per model cycle. The difference between the number of annual vials used in the MAA and in the model amounts to [redacted] less in ESA treatment costs in the first year of the model, when compared to ESA costs in the MAA. The total treatment cost for ESA in the model (and therefore the respective underestimation compared to the MAA) changes every year in the model, as every year (i.e. every model cycle) there will be a different distribution of patients across the different WC categories (and respective weights).

Given that the movement of ESA patients across WC categories is reduced throughout the model (Figure 11), the baseline weight distribution in each WC category is one of the key model drivers. Equally, the proportion of patients allocated to each WC state at baseline and at the end of Year 1 in the model are also key drivers of the economic results.

Figure 11. Markov trace in ESA arm



If the MAA data were to be analysed with a complete case analysis approach (as discussed in Section 3.7 and 3.8 of the report), the ERG considers that the baseline weight per WC category is likely to change. Changing the method of analysis for the clinical data might also influence the outcome around weight change throughout the MAA period. Nonetheless, given the ERG's consideration that MOR-005 is a more robust source of evidence to estimate ESA's effectiveness, the ERG recommends that the weight data used to estimate treatment costs in the model is sourced from MOR-005. Additionally, the ERG cautions the company to adjust the weight of patients in every model cycle in order to satisfy the average number of vials used in MOR-005 (or in the MAA if the company does not change the source for weight data in the model).

Furthermore, the company included a 20% discount for ESA in their base case based on an assumption that VAT would not apply to home infusion drugs. This was previously removed in the original ERG report for the HST2 as according to the NICE methods guide, VAT should be excluded from all economic evaluations, therefore there would be no difference between the drug cost between home and hospital care. Thus, the ERG recommends that the company removes the 20% discount from its base case results.

4.2.9.2 Administration costs

Elosulfase alfa is administered as a weekly home infusion. The administration cost for ESA in the company's base case model is £207 per week, based on the NHS reference cost code QZ14B (vascular access for renal replacement therapy without CC) from 2013/14 (as per CS, Table 91). During the clarification stage, the ERG asked why a more recent cost was not used. In response, the company said the cost of administration had been updated in the model to £213 to reflect the 2016/2017 tariff. Nonetheless, the company did not change the administration cost in the model, which remained £207.

The total cost of administration for ESA was estimated as a weighted average based on the proportion of home infusions that required supervision by a nurse and the proportion of infusions received in the hospital. The company assumed that 90% of infusions will happen at home, while 10% will be administered in the hospital. Out of the 90% of patients who received their infusion at home, the company considered that [redacted] of patients are capable of self- (or carer-) administration of ESA, while [redacted] require a nurse-supervised administration.

In response to a clarification question, the company reported that the cost for home infusion is based on NHS England negotiations with homecare companies through the national framework for all ERT infusions. The cost used by the company was of [redacted] per infusion. For patients not needing a nurse, the cost of four hours of nurse supervision (PSSRU 2019, nurse cost per hour is £40) was deducted from the total [redacted] to arrive at the cost of [redacted] per infusion. The total home cost infusion was thus, £239.11.

The final administration cost in the model is given as [redacted]. For 90% of the patients who receive ESA at home, the £239.11. administration costs are applied. For the remaining 10% of patients who receive ESA in hospital, the company have assigned the original administration cost of £207.

ERG critique

The ERG asks that the company replaces the £207 with the updated £213 estimate in the model as the company did not change this in the analysis.

Without having access to the resource use incorporated in the NHS England negotiated cost for home infusions for ERT infusions the ERG cannot validate the company's estimation of the cost of home infusion derived by subtracting 4 hours of nurse supervision time from the cost of home

infusion. Therefore, the ERG recommends that the company provides further clarification on the resource use included in the cost for ERG home infusions.

4.2.9.3 Surgical costs

Surgical rates were applied in both arms of the model and assumed to not vary across SoC and ESA patients. More details on surgeries in the model are given in Section 4.2.6.3 of the ERG report. The costs of surgery were taken from the 2018/19 NHS reference cost schedule and are detailed in Table 41.

Table 41. Surgical costs (adapted from Table 94 in CS)

Variable	Value	Range or 95% confidence interval	Source
Cervical Fusion Operation	£20,029	All costs were varied by ±10%	NHS Reference Costs 2018/2019 HC51E and HC51D - Complex Instrumented Correction of Spinal Deformity, 18 years and under, with CC Score 3+ and 0-2; average taken of both
Genus Valgum surgery	£4,203	All costs were varied by ±10%	NHS Reference Costs 2018/2019 Intermediate Knee Procedures for Trauma (<18, >18; CC Score 0,1,2+)
Spinal decompression surgery	£13,631	All costs were varied by ±10%	Uplifted 2006 cost to 2020 (using https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator)
Hip surgery	£6,040	All costs were varied by ±10%	NHS Reference Costs 2018/2019 - HN12F Very Major Hip Procedures for Non-Trauma with CC Score 0-1
Lower spine surgery	£13,631	All costs were varied by ±10%	Assumed same as spinal decompression
Aortic valve replacement	£7,908	All costs were varied by ±10%	NHS Reference Costs 2018/2019 - EC13C Major Procedures for Congenital Heart Disease with CC Score 0-3
Tonsillectomy	£1,913	All costs were varied by ±10%	NHS Reference Costs 2018/2019: CA60C Tonsillectomy 4 years and over
Ear tube placement	£1,211	All costs were varied by ±10%	NHS Reference Costs 2018/2019: CA35B Insertion of Grommets, between 2 and 18 years
Corneal replacement.	£3,035	All costs were varied by ±10%	NHS Reference Costs 2018/2019: BZ61B Complex, Cornea or Sclera Procedures, with CC Score 0-1

Cataract surgery	£2,581	All costs were varied by ±10%	NHS Reference Costs 2018/2019: BZ32B Intermediate, Cataract or Lens Procedures, with CC Score 0-1

Abbreviation: CC, critical care.

4.2.9.4 Adverse event costs

The company states that the costs of AEs in the model were indirectly captured as part of the administration costs in the model given that AEs were assumed to be controlled through the premedication drug regimen. The data for the proportion and type of premedication drugs comes from the MOR-004 study and are shown, alongside the unit costs, in Table 42. The weighted average cost of premedication per cycle is £3.09 per year.

Table 42. Premedication drugs and costs

Premedication drug	Percentage of patients	Unit cost
Paracetamol	56.90%	£0.39
Loratadine	34.50%	£0.25
Desloratadine	13.80%	£0.52
Prednisolone/ Prednisone	25.90%	£0.6
Hydrocortisone	8.60%	£6.48
Prednisolone Sodium Succinate	6.90%	£4.83
Hydrocortisone Sodium Succinate	5.20%	£9.16
Ranitidine/Ranitidine Hydrochloride	25.90%	£1.35
Cetirizine/Cetirizine hydrochloride	22.40%	£0.21
Diphenhydramine/Diphenhydramine Hydrochloride	17.20%	£3.03
Clemastine Fumarate	6.90%	£7.33
Chlorphenamine/ chlorphenamine maleate	12.00%	£0.16
Hydroxyzine	8.60%	£2.1
Lidocaine	6.90%	£4.72
Ibuprofen	5.20%	£0.75

Source: eMIT, British National Formulary
Abbreviations: eMIT, electronic market information tool

ERG critique

Given its low cost, the premedication assumed in the model is unlikely to have an impact on the final ICER. Despite this, as discussed in section 4.2.7, there is a significant subset of patients in both MOR-004 (reported in HST2) and the MAA safety dataset who have AEs associated with administering ESA, for whom premedication is not sufficient to control the event.

4.2.9.5 Resource use costs

Health state costs were calculated per annual cycle in the model. Resource use was determined by the company's clinical experts via a Delphi process and is reported in Table 93 of the CS.

Wheelchair costs consist on an annual cost of £196.06. The latter was the same regardless of the WC state, as the relevant resource was the WC acquisition cost. Wheelchair unit costs were sourced from PSSRU unit costs of health and social care 2019 and were applied as a weighted cost based on the type of WC used (Table 43). The company assumed that the split between the three types of WC was equal.

Table 43. Wheelchair cost components

Wheelchair	Percentage use	Cost
Self or attendant propelled	34.0%	£70.00
Active user	33.0%	£174.00
Powered	33.0%	£348.00

ERG critique

The ERG's clinical experts' view was that the company's estimates of resource use in the different health states were not reflective of UK's clinical practice, as for example, MPS IVA patients do not see their GP after diagnosis, but instead are followed by a specialist in a hospital-based clinic. Another issue identified by the ERG's clinical experts was the considerable underestimation of resource use in the end stage disease state by the company.

At clarification the company provided updated costs for specialist care and palliative care, however it did not supply the cost codes used in calculating these, and so the ERG has been unable to validate

these in the reference cost schedule. The ERG recommends that the company provides sources for these costs.

The ERG's clinical experts' proposed resource use is reported in Table 44. The unit costs applied to the resource use estimates and respective sources are given in Table 45. The impact of the change in resource use on the final health state costs is provided in Table 46. The ERG recommends that the company includes the alternative resource use proposed by the ERG's clinical experts as a scenario in the updated model once the clinical data have been re-analysed.

Table 44. ERG clinical experts resource use assumptions

Resource	Asymptomatic	No use wheelchair	Sometimes wheelchair	Wheelchair dependent	Paraplegic	End stage
Specialist visit	1.9	2.1	3.2	4.3	6.2	6.2
Palliative care	0.0	0.0	0.0	0.0	0.0	4.0
A&E visit	0.0	0.0	0.0	0.3	0.3	0.0
Pulmonary complication visit	1.0	1.0	1.0	1.0	1.0	1.0
Pain management clinic visit	0.0	0.0	0.0	0.0	0.0	4.0
Mental health specialist visit	1.0	1.0	1.0	1.0	1.0	1.0
Cardiology specialist visit	1.0	1.0	1.0	1.0	1.0	1.0
Ophthalmology	1.0	1.0	1.0	1.0	1.0	1.0
ENT specialist visit	1.0	1.0	1.0	1.0	1.0	1.0
Ventilation	0.0	0.0	0.0	0.0	0.0	1.0

Table 45. Resource use unit costs

Unit cost	Value	Source
Specialist visit	£109.25	Not provided by the company
Palliative care	£202.00	Not provided by the company

A&E visit	£156.00	NHS Reference Costs 2018/2019 average of all A&E costs
Pulmonary complication visit	£157.00	NHS Reference Costs 2018/2019 Respiratory medicines Outpatient appointment
Pain management clinic visit	£650.00	Expert opinion, Delphi Process
Mental health specialist visit	£282.00	NHS Reference Costs 2018/2019 Children and Adolescent Mental Health Services, Outpatient Attendances
Cardiology specialist visit	£139.00	NHS Reference Costs 2018/2019 Cardiology Outpatient appointment
Ophthalmology	£98.00	NHS Reference Costs 2018/2019 Ophthalmology Outpatient appointment
ENT specialist visit	£107.00	NHS Reference Costs 2018/2019 ENT Outpatient appointment
Ventilation	£3,071.00	NHS Reference Costs 2018/2019: PK72C Paediatric Metabolic Disorders with CC Score 0 (using ICD10 E762 + OPCS E851)

Abbreviations: ENT, Ear Nose Throat; CC, critical care.

Table 46. Health state costs

Health state	Company base case cost	ERG clarification cost scenario
Asymptomatic	£227.10	£990.58
No use wheelchair	£628.21	£1012.43
Sometimes wheelchair	£906.50	£1132.60
Wheelchair dependent	£1471.71	£1299.58
Paraplegic	£1786.27	£1507.15
End stage	£3071.00	£7939.35

4.2.9.1 Carer costs

Carer costs have been included in the company's base case results and were calculated based on the hours of caregiving reported in Hendriksz *et al.* 2014.[63] The hourly cost of care was assumed to be

£28, sourced from the PSSRU Unit Costs of Health and Social Care 2019. The company assumed that 50% of the cost of caring would be borne by the parents or legal guardians of patients.

The company assumed that asymptomatic and NWC patients would have the same caring burden, and that the WCD, paraplegic and pre-death states would also have the same associated caring needs.

The carer-related cost per model cycle was calculated by multiplying the number of hours needed per health state by the hourly cost of home caring. The annual costs associated with caring are given in Table 47.

Table 47. Caring costs

Health state	Hours per day	Costable hours per cycle	Total cost per cycle
Asymptomatic	1.5	273	£7,644.00
No use Wheelchair	1.5	273	£7,644.00
Sometimes use wheelchair	4	728	£20,384.00
Wheelchair dependent	14	2,548	£71,344.00
Paraplegic	14	2,548	£71,344.00
Pre-death	14	2,548	£71,344.00

ERG critique

Carers costs are the key driver of SoC costs in the model, amounting to [redacted]% of total costs for the comparator arm. When carer costs are removed from the model, SoC costs decrease by [redacted] while ESA costs decrease only by [redacted]. This is related to the company's assumptions on the use of WC in the SoC arm, where patients are much more dependent than patients in the ESA arm.

5 Cost effectiveness results

5.1.1 *Company's cost effectiveness results*

The company's base case deterministic ICER (discounted) for ESA versus SoC is provided in Table 48. The company's base case included the costs and QALY decrements for carers of patients. According to the company's analysis, ESA is expected to extend patients' lives by around [redacted] years (undiscounted) compared to SoC. This translates to an incremental quality-adjusted life year (QALY) gain for elosulfase alfa of [redacted] QALYs, and an incremental cost-effectiveness ratio (ICER) of [redacted].

Table 48. Company's deterministic base case results (discounted except for life years gained)

Interventions	Total Costs (£)	Total LYG undiscounted	Total QALYs	Incremental costs (£)	Incremental LYG undiscounted	Incremental QALYs	ICER (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Elosulfase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

When carer outcomes are excluded from the analysis, the incremental QALYs increase slightly to 20.1, as do the incremental costs, leading to an ICER of [redacted] per QALY gained. The company's deterministic ICER (discounted) for ESA versus SoC is provided in Table 49, excluding carer outcomes.

Table 49. Company's deterministic results without carer outcomes (discounted except for life years gained)

Interventions	Total Costs (£)	Total LYG undiscounted	Total QALYs	Incremental costs (£)	Incremental LYG undiscounted	Incremental QALYs	ICER (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Elosulfase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The undiscounted QALY gain in the company's base case analysis amounts to [redacted] while the undiscounted QALY gain in the company's results excluding carer outcomes amounts to [redacted] QALYs.

5.1.2 *Company's sensitivity analyses*

The ERG did not report the results of the company's sensitivity analysis as these are all based on the flawed analysis of clinical data in the model, rendering the results meaningless until the data are re-analysed.

Nonetheless, the ERG has concerns around the company's method used to run the probabilistic sensitivity analysis (PSA). As it stands, the ERG does not consider that the company's PSA is robust enough to explore uncertainty in the cost-effectiveness results. All parameters in the model were only varied by +/- 10% around their mean values, even when real data on standard errors were available (as for example in the FVC and 6MWT mean values used in the SoC arm).

Furthermore, the ERG questions the validity of some of the choices of distributions to explore parameter uncertainty. For example, the same parameter (the probability of being a mild decliner or a non-responder) was modelled with a normal; a beta and a Dirichlet distribution depending on the year in the model or the WC state (Table 50). Without any justification, the choice of 3 different distributions to model the same parameter cannot be validated by the ERG. Additionally, the company used a normal distribution to assess the uncertainty around relative risks; proportions; and some probabilities in the model. It would have been more appropriate to assess the latter with a lognormal distribution (for relative risks); a beta or Dirichlet distributions for proportions and probabilities.

Therefore, the ERG recommends that the company revisits the distributions used to assess parameter uncertainty and uses the 95% CIs around all mean estimates used in the model (where available).

Table 50. PSA parameters and distributions

Variable	Distribution
Patient weight in each health state	Normal
Efficacy - relative risks of mortality	Normal
Efficacy – proportion of long-term stabilisers, mild decliners and non-responders in year 1 and in year 2+ in the model	Normal
Efficacy – decline in patients' outcome measures (in years)	Normal

Efficacy – delay in patients' surgery (in years)	Normal
Costs	Normal
Utilities	Normal
Carer hours	Normal
Carer costs	Normal
Probability of surgery	Beta
Probability of surgery (aortic valve replacement; tonsillectomy; ear tube replacement; corneal replacement and cataract surgery) success or surgery-related death	Beta
Efficacy – proportion of long-term stabilisers, mild decliners and non-responders in year 1 and in year 2+ in the model	Beta
Efficacy – proportion of long-term stabilisers, mild decliners and non-responders in year 1 and in year 2+ in the model	Dirichlet
Probability of surgery (cervical fusion; genus valgum; spinal decompression; lower spine and hip surgery) success or surgery-related death	Dirichlet

6 Additional economic analysis undertaken by the ERG

In this section the ERG provides a list of model corrections and scenario analyses to be conducted once the company has re-analysed the clinical data used in the model according to the complete case analysis method as discussed in detail in Section 3.8. The ERG also reiterates that the preferred source of clinical data to be used in the model is the matched MorCAP1 and the QW-QW MOR-005 data, for SoC and ESA, respectively.

6.1 Model corrections recommended by the ERG

The ERG's preliminary investigation of the company's model indicated that the following corrections are necessary:

1. Inclusion of cycle 0 outcomes throughout the model, without a half-cycle correction, and with a discount rate of 1 (so no discount should be used in cycle 0). Cycle 1 in the model should include the half correction from cycle 0 to cycle 1, and outcomes should start being discounted in this cycle. This approach eliminates the need to multiply undiscounted outcomes by 2 in the first cycle of the model, which should be removed;
2. The company's assumption of a 5-year delay on patients becoming symptomatic is actually a 6-year delay when compared to SoC patients given that patients on ESA were assumed not to progress from the asymptomatic state during the first year of the model. This should be corrected to reflect the 5-year delay intended by the company in their base case analysis;
3. The ERG found an error in the economic model as patients in the NWC (or SWC) state were being given a probability of cervical fusion of 0% instead of the 38% intended by the company (for example, please see cell BS14 in "PF_comparator_Sym" tab, where the "p_FusionOP_Sometimes" needs to be replaced with "p_FusionOP_never" in the formula);
4. The company's scenario analysis where mortality is linked to decreased %FVC in the model is not working;
5. The ERG asks that the company replaces the £207 administration cost with the updated £213 estimate in the model as the company did not change this in the analysis;
6. The ERG recommends that the company revisits the distributions used to assess parameter uncertainty in the PSA and uses the 95% CIs around all mean estimates used in the model (where available).

6.2 Exploratory and sensitivity analyses recommended by the ERG

The ERG recommends that the company provides additional exploratory analysis as flexible options in the Excel model. This will allow investigating the impact of adding or removing these analyses, and crucially, combining them to generate the committee's preferred set of analyses.

Once the clinical data have been re-analysed and included in an updated economic model, the ERG proposes that the company undertakes the scenario analyses listed below – the ERG has included the section where each scenario has been discussed, and where more details can be found around the ERG's issues. Some of these scenarios have been requested by the ERG during the clarification stage and have been provided by the company as a response. The ERG listed these again for completeness.

- Modelling approach:
  1. Given the weak correlation seen in the MAA data between improvements in 6MWT and FVC measures and improvement in WC status; and the availability of reasonably robust studies establishing the relationship of standardised endurance and respiratory measures (such as the 6MWT and FVC) with patients' QoL, the ERG remains unconvinced that a WC-based economic model provides the most robust approach to assess the cost-effectiveness of ESA in MPS IVA patients, therefore, the ERG asks that the company reconsiders their modelling approach (see Section 4.2.4.1);
  2. If a model based on WC use is to be maintained, the ERG recommends that the thresholds for change in WC are revaluated and made consistent with the underlying clinical data. The ERG recommends that once the MorCAP1 and MOR-005 data are re-analysed, the company re-defines the thresholds used to determine WC use change, so that the latter are consistent with the baseline clinical data observed in the pivotal studies (see Section 4.2.4.1 and Section 4.2.6.2).
  3. Given that the long-term benefits associated with ESA remain uncertain, particularly its impact on patients' survival the ERG recommends that the company conducts a scenario analysis where a 3.5% discount rate is used in the model for both costs and benefits (see Section 4.2.5).
- Time to onset of disease symptoms:
  4. The ERG notes that the Montaño *et al*. study reported that the mean age of onset of disease was 2.1 years, with initial symptoms recognised between 1 and 3 years. Therefore, the ERG

recommends that the company undertakes a scenario analysis where SoC patients take 2 years to become symptomatic (see Section 4.2.6.2).

- Use of WC data in the model:

5. The ERG recommends that the WC data used in the first year of the model is the annual probability of patients going from their baseline WC state to their respective WC state at the end of year 1, in both MorCAP1 and MOR-005 (see Section 4.2.6.2);
6. The ERG recommends that the company uses the WC annual data (year 1 to year 2; and year 2 to year 3, if possible) available from MorCAP1 to estimate transition probabilities between the NWC; SWC; and WCD states in the model for the first 2 or 3 years and provides these data (see Section 4.2.6.2);
7. The ERG recommends that the company uses the WC annual data (year 1 to year 2; and year 2 to year 3, if possible) available from MOR-005 to estimate transition probabilities between the NWC; SWC; and WCD states in the model for the first 2 or 3 years and provides these data (see Section 4.2.6.2);

- Use of FVC and 6MWT data in the model:

8. The ERG recommends that the values used to estimate the change in 6MWT and FVC outcomes for SoC patients are taken from the re-analysis of the MorCAP1 and that the values used are based on the available annual estimates, similar to what has been requested for changes in WC use (see Section 4.2.6.2);
9. The ERG recommends that the values used to estimate the change in 6MWT and FVC outcomes for ESA patients are taken from the re-analysis of the MOR-005 and that the values used are based on the available annual estimates, similar to what has been requested for changes in WC use (see Section 4.2.6.2);
10. The ERG recommends that the company conducts a comparison of the annual changes in 6MWT and FVC outcomes in MorCAP1 and MOR-005 and assesses if additional scenario analysis should be conducted. For example, if the data signals thar ESA might not have a benefit against SoC for NWC patients (as seen in the ERG's preliminary analysis), the ERG recommends including a scenario in the model where ESA does not have a benefit against SoC for NWC patients (see Section 4.2.6.2);

- Estimation of mortality:

11. The ERG recommends that the company uses the approach employed in their scenario analysis where mortality is linked to FVC decrements as their base case analysis (see Section 4.2.6.4);

12. The ERG recommends that the company uses the improvement in FVC over time observed in MOR-005 instead of MOR-001/002 to estimate the impact of ESA on mortality, and the FVC data from MorCAP1 to estimate mortality in the SoC arm (see Section 4.2.6.4);
13. The ERG considers that the RR of 1.12 used by the company for every 10% decrement in FVC is incorrectly used, and instead recommends that the company applies the 1.15 rate ratio from Neas and Schwartz, 1988 study and applies it correctly to the general population mortality (i.e. by exponentiation and not multiplication) – see Section 4.2.6.4.

- Estimation of surgery:

14. The ERG recommends that the company includes a scenario analysis in the model where only patients in the NWC and the SWC states receive cervical fusion surgery (and have the potential associated complications leading to paraplegy) – see Section 4.2.6.6;
15. The ERG recommends that the company conducts a scenario analysis where the assumption of surgery delay associated with ESA is removed from the model (see Section 4.2.6.6);
16. The ERG recommends that the company conducts a scenario analysis to explore the impact of removing the assumption of faster recovery from surgery for ESA patients from the model (see Section 4.2.6.6);

- Quality of life analysis (see Section 4.2.8):

17. The ERG's preferred source for utilities values is the Hendriksz *et al*. 2014[63] burden of disease study for patients with MPS IVA, the same source used in the original company submission for the HST2. Therefore, the ERG recommends that the company undertakes a scenario analysis where:
    a. The same utilities values from the HST2 are used in the model;
    b. All WC states have the same utility in both treatment arms, and utility increments associated with gains in the 6MWT and FVC outcomes observed for ESA are estimated;
    c. The FVC and 6MWT increments used are those underpinning the treatment effectiveness analysis and the clinical data used in the model.
18. Given the likely uncertainty around the FVC and 6MWT benefits associated with ESA resulting from the comparison of MorCAP1 and MOR-005 data, the ERG also recommends an exploratory analysis where the same utility values associated with WC states are used in both arms of the model and no utility increments are assumed for ESA. In this scenario, patients' gain in quality of life comes from changes in WC use, and the movement across these states in both treatment arms.

- Costs:

19. The ERG recommends that the weight data used to estimate treatment costs in the model is sourced from the re-analysed MOR-005 data (see Section 4.2.9.1);
20. The ERG cautions the company to adjust the weight of patients in every model cycle in order to satisfy the average number of vials used in MOR-005 (or in the MAA if the company does not change the source for weight data in the model) (see Section 4.2.9.1);
21. The ERG recommends that the company removes the 20% VAT discount from its base case results (see Section 4.2.9.1);
22. The ERG recommends that the company includes the alternative resource use proposed by the ERG's clinical experts (Table 44) as a scenario analysis (see Section 4.2.9.5).

6.3 List of recommended clarifications from the company

The ERG also produced a list of issues requiring additional clarification from the company. Some of these pertain to the company's base case assumptions and are around the MAA data.

1. The ERG recommends that the company explains how the WC data was captured in MorCAP1, especially for the WCD state; and how the WC data captured in MorCAP1 were allocated to the same WC categories used in the model;
2. The ERG recommends that the company undertakes a qualitative comparison of all years with transition probability data available from MorCAP1, and MOR-005, once the data have been re-analysed, and ensures that the model long-term assumptions are consistent with these data;
3. The ERG requests that the company explains how the 4-month delay in surgery associated with ESA was estimated in the model. The ERG's preliminary analysis was that the company used time to first surgical event in the QW-QW arm (approximately 52 weeks) minus time to first surgical event in the PBO-QW (approximately 36 weeks) to arrive at the 4-month (16 weeks) delay;
4. The ERG recommends that the company re-analyses the MAA EQ-5D data with the complete case analysis method, and discusses the changes observed in QoL for MAA patients in light of the new results;
5. The ERG remains unclear as to how the company estimated the mean gain in 6MWT in the ESA arm (60m) and increase in mean FVC (0.054L) to derive utility increments. The ERG

recommends that a clear explanation on the sources used, and the calculations and assumptions undertaken are provided;

6. Without having access to the resource use incorporated in the NHS England negotiated cost for home infusions for ERT infusions the ERG cannot validate the company's estimation of the cost of home infusion derived by subtracting 4 hours of nurse supervision time from the cost of home infusion. Therefore, the ERG recommends that the company provides further clarification on the resource use included in the cost for ERG home infusions;
7. At clarification the company provided updated costs for specialist care and palliative care, however it did not supply the cost codes used in calculating these, and so the ERG has been unable to validate these in the reference cost schedule. The ERG recommends that the company provides sources for these costs.

6.4 Conclusions of the cost effectiveness sections

Based on the company model available to the ERG at the time of writing, the ERG considers that that the company's economic analysis is unfit for decision making. The ERG's investigation led to the conclusion that a re-analysis of the MorCAP1 data is required, together with the replacement of the MAA data by the MOR-005 data in the model.

The ERG remains concerned that a WC-based economic model does not provide the most robust approach to assess the cost-effectiveness of ESA in MPS IVA patients. In the CS it is discussed how, based on long-term outcomes from the MAA dataset, positive changes from baseline in 6MWT and FVC outcomes are an appropriate method to reflect changes in WC dependency. Based on that observation, the company decided to use WC use as the main modelling outcome. The ERG considers that the exact opposite argument should be made – given that endurance (measured through 6MWT) and pulmonary outcomes (measured through FVC) have been deemed the most relevant and sensitive outcomes by patients and clinical experts to assess disease progression and quality of life, **and** have been found by the company to be poor predictors or poorly correlated with changes in WC use, then using WC use as the key outcome in the economic analysis is inappropriate to capture the cost-effectiveness of ESA and is unfit for decision making.

If a WC-based model is to be used, the ERG recommendation is that more WC, 6MWT, and FVC data from MorCAP1 and MOR-005 are incorporated in the model and crucially, that the WC data collected from the ESA and comparator studies are consistent and comparable, and that the thresholds defined for changes in WC states in the model are representative of the underlying

clinical data. Equally, the ERG notes that it has not seen any evidence to substantiate the company's assumption that ESA patients do not become more WC dependent after year 1 in the model. The assumption that [redacted] of ESA patients do not have disease progression in the model is likely to be one of the key drivers of the company's base case economic results and, therefore, the ERG requests that the company ensures that any long-term assumptions of treatment effectiveness made in the model are consistent with the underlying clinical data.

The ERG's preliminary investigation of the IPD concluded that the company underestimated the cost of ESA in the model. As the company used the average weight of patients in each WC state and patients were not evenly distributed across the WC categories at baseline (5% asymptomatic; 40% NWC; 50% SWC; and 5% WCD), the weighted average of patients' weight at the beginning of the model was lower than the average weight observed in the MAA population. Given that the movement of ESA patients across WC categories is reduced throughout the model, the baseline weight distribution in each WC category is one of the key model drivers. Equally, the proportion of patients allocated to each WC state at baseline and at the end of year 1 in the model are also key drivers of the economic results. Therefore, the ERG cautions the company to adjust the weight of patients in every model cycle in order to satisfy the average number of vials used in MOR-005 (or in the MAA if the company does not change the source for weight data in the model).

The ERG remains unclear on the company's proposition around the value of ESA on improving patient outcomes and notes that the additional analysis of the treatment effectiveness data should be used to inform the economic analysis and shed some light on the benefits of ESA.

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8 Appendices

8.1 Company's quality assessment of MOR-005

Table 51. Company quality assessment of MOR-005 (Hendriksz et al. 2016c; reproduced from CS, Table 32)

Characteristic	Response	How is the question addressed in the study?
Was randomisation carried out appropriately?	Unclear	The exact method of generating the randomisation sequence was not reported. Only those patients who had been on placebo in MOR-004 were re-randomised without stratification (1:1 ratio) to either ESA 2.0 mg/kg QW or QOW. Patients randomised in MOR-004 to an ESA treatment arm remained on that treatment in MOR-005 part 1. At a specific date (01-Dec-2012), in MOR-005 part 2 (the open label extension), all patients were switched to ESA 2.0 mg/kg/QW, the recommended dose after review of final results from MOR-004 and the DMC.
Was the concealment of treatment allocation adequate?	Unclear	Concealment not specified
Were the groups similar at the outset of the study in terms of prognostic factors?	No	Randomisation on entry to MOR-005 was not stratified (as MOR-005 objective was to evaluate long-term efficacy and safety of active treatment, and to enable patients previously randomised to placebo to receive ESA until marketing authorisation allowed access to commercial product) and a chance imbalance occurred in MOR-005 baseline characteristics (age and endurance measures) resulting in better 6MWT and 3MSCT results for (previously on placebo) patients now on ESA 2.0 mg/kg QOW than for (previously on placebo) patients now on ESA 2.0 mg/kg QW.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Described as double-blind. Further, masking described as quadruple: participant, care provider, investigator, outcomes assessor.
Were there any unexpected imbalances in drop-outs between groups?	No	Discontinuations were 1/56 (1.8%) from Part 1 and 1/56 (1.8%) from Part 2 in ESA 2.0 mg/kg QW arm (weekly dose in both MOR-004 and MOR-005) and 0/59 (0%), 0/29 (0%) and 0/29 (0%) in ESA 2.0 mg/kg QOW (QOW dose in both MOR-004 and MOR-005) and placebo-QOW and placebo-QW cohorts.

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No indication of selective reporting
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT analysis performed. MPP results also presented. MPP population excluded patients who had orthopaedic surgery and those not complying with protocol recurrently. Missed infusions were used to indicate compliance; patients missing ≥20% of their scheduled ESA infusions during MOR-005 were classified as non-compliant (14 patients) and excluded from MPP population. Total excluded from MPP population 49 patients.
Additional info	–	Authors comment that variable timing of transition to weekly dosing (from week 36 to week 96) precludes comparison of dosing regimens. Comparison further made difficult by small sample sizes in cohorts of patients originally randomised to placebo. Hence MPP population compared to MorCAP data.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; DMC, data monitoring committee; ESA, elosulfase alfa; ITT, intention to treat; MPP, modified per protocol; QOW, every other week; QW, weekly.

8.2 Methods of ESA studies

8.2.1 MOR-004

Table 52. Summary of methods for MOR-004

Characteristic	Description
Study name	MOR-004
Objective	To evaluate the efficacy and safety of elosulfase alfa (BMN 110) 2.0 mg/kg/week and 2.0 mg/kg/every other week in patients with MPS IVA (Morquio A Syndrome).
Location	Multinational (17 countries).
Design	Phase 3, three-arm, randomized, masked, placebo-controlled, multinational study carried out over 24 weeks.
Duration of study	Start date: February 2011. Date of completion: August 2012.
Patient population	Patients with MPS IVA aged 5 years and older and with 6MWT distance between 30 metres and 325 metres.
Sample size	177 patients
Inclusion criteria	•At least 5 years of age. •Documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA. •Willing and able to provide written, signed informed consent, or in the case of patients under the age of 18 (or 16 years, depending on the region), provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures.

	•Must meet the study entrance requirements for the 6-minute walk test. •Sexually active patients must be willing to use an acceptable method of contraception while participating in the study. •Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study.
Exclusion criteria	•Previous hematopoietic stem cell transplant. •Previous treatment with elosulfase alfa. •Has known hypersensitivity to any of the components of elosulfase alfa. •Major surgery within 3 months prior to study entry or planned major surgery during the 24-week treatment period. •Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study. •Use of any investigational product or investigational medical device within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments. •Concurrent disease or condition, including but not limited to symptomatic cervical spine instability, clinically significant spinal cord compression, or severe cardiac disease that would interfere with study participation or safety as determined by the Investigator. •Any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study.
Intervention(s) (n =) and comparator(s) (n =)	**Elosulfase alfa** Arm 1 (N=58) received elosulfase alfa weekly given as an intravenous infusion at a dose of 2.0 mg/kg administered over a period of approximately 4 hours. Arm 2 (N=59) received elosulfase alfa every other week as an intravenous infusion at a dose of 2.0 mg/kg administered over a period of approximately 4 hours, with infusions of placebo on alternating weeks. **Placebo** Arm 3 (N=59) received placebo given as an intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of elosulfase alfa administered over a period of approximately 4 hours once a week.

Duration of follow-up, participants lost to follow-up information	MOR-004 was limited to a 24 week treatment period, after which patients could enrol in the long-term follow-up study, MOR-005. Of the 177 people randomised, one person randomised was not treated and was excluded from analysis because the diagnosis of MPS IVA was not confirmed. Of the 176 people forming the modified ITT population, 175 completed MOR-004, with 173 patients continuing into MOR-005.
Statistical tests	MOR-004 was designed to test the superiority of elosulfase alfa compared with matching placebo on the primary efficacy outcome of the mean change in 6MWT from baseline to week 24.[67] Assuming a standard deviation of 65 m, a power of 90%, a two-sided significance level of 5%, a 1:1:1 randomization scheme, and an adjustment for multiplicity using the Hochberg method, approximately 162 patients (or 54 patients per group) valid for ITT or safety analyses would be required to detect a mean difference between elosulfase alfa (either the weekly or alternate-weekly regimens) and placebo of 40 m. There was no mention of invalidity rate considerations in the calculation. Outcomes were analysed using a modified mITT principle, which included all randomized patients who received at least one dose of study drug. No formal interim analysis was planned. The primary analysis of the primary endpoint was the analysis of covariance (ANCOVA) of the Week 24 change from baseline in the 6MWT measurement using a model with treatment, age stratification (5–11, 12–18, ≥ 19 years), and baseline 6MWT stratification (≤ 200 metres and > 200 metres) as factors. Each active treatment group was compared to the placebo group using contrasts and P values calculated using the t test. Least squares means and confidence intervals for the two treatment effects were also provided. There were only 2 missing assessments of 6MWT, and the two values were imputed using multiple imputation.
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline in endurance as measured by the 6MWT.
Secondary outcomes (including scoring methods and timings of assessments)	•Change from baseline in endurance as measured by the 3-minute stair climb test. •Percent change from baseline in urine keratan sulphate normalized for urine creatinine.
Exploratory efficacy endpoints	Tertiary outcomes listed as: •Pharmacokinetics; •Respiratory function tests (MVV, FVC, FEV_1, FIVC);

	•MPS HAQ; •Biomarkers (inflammation, bone and cartilage metabolism); •Anthropometry; •Radiographs; •Audiometry examinations; •Echocardiograms; •Corneal clouding.

Abbreviations: 6MWT, 6-minute walk test; FEV_1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; ITT, intention to treat; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVA, mucopolysaccharidosis IVA; MVV, maximum voluntary ventilation.

8.2.2 MOR-005

Table 53. Summary of methods for MOR-005

Characteristic	Description
Study name	MOR-005
Objective	To evaluate the long-term efficacy and safety of elosulfase alfa 2.0 mg/kg/week and 2.0 mg/kg/every other week in patients with MPS IVA.
Location	Multinational (20 countries).
Design	MOR-005 is a Phase 3 extension of MOR-004 involving people who completed MOR-004. MOR-005 is ongoing and is scheduled to be carried out over 240 weeks, not including time spent in MOR-004. However, no patient completed the 240 weeks of MOR-005 as they switched to commercially available therapy. Therefore, all analyses from MOR-005 presented in the CS and the publications are based on week 120 follow-up. MOR-005 comprises two parts.

	Part 1 was a randomised, quadruple-blind component in which people randomised to placebo in MOR-004 were re-randomised (1:1) to one of the elosulfase alfa treatment regimens. Those randomised to elosulfase alfa in MOR-004 carried on with their allocated treatment. Part 1 continued until the optimal dosing regimen for elosulfase alfa had been determined, which was based on the final primary efficacy analysis from MOR-004 (completed 30/11/2012). Thus, there are four cohorts in Part 1 of MOR-005: QW-QW; QoW-QoW; placebo-QW; placebo-QoW. The last study visit assessments for MOR-004 constituted baseline data for MOR-005. The first study drug dose occurred on Week 0 of MOR-005, which was the same as the last visit (Week 24) of MOR-004. In Part 2 (initiated 1/12/2012), all patients transitioned onto elosulfase alfa 2 mg/kg/weekly for the open label phase. Two people from MOR-004 did not enrol in MOR-005. In MOR-005 patients had access to surgery, which is in contrast to MOR-004 where surgery was not permitted. Timing of transition to weekly dosing depended on study enrolment timing and ranged from week 36 to 96 in MOR-005, that is, 50 to 120 weeks from the start of MOR-004.
Duration of study	Start date: 01/12/2012 Date of completion: Ongoing
Patient population	Patients with MPS IVA aged 5 years and older and must have completed MOR-004.
Sample size	Part 1: 173 Part 2: 169
Inclusion criteria	•Must have completed MOR-004. •Is willing and able to provide written, signed informed consent. Or in the case of patients under the age of 18 (or other age as defined by regional law or regulation), provide written assent (if required) and have written informed consent, signed by a legally authorize representative, after the nature of the study has been explained, and prior to performance of research-related procedures. •If sexually active, must be willing to use an acceptable method of contraception while participating in the study. •If female, of childbearing potential, must have a negative pregnancy test at Baseline and be willing to have additional pregnancy tests done during the study.
Exclusion criteria	•Is pregnant or breastfeeding, at Baseline, or planning to become pregnant (self or partner) at any time during the study.

	•Has used any investigational product (other than elosulfase alfa in MOR-004), or investigational medical device, within 30 days prior to Baseline; or is required to use any investigational agent prior to completion of all scheduled study assessments. •Was enrolled in a previous elosulfase alfa study, other than MOR-004. •Has a concurrent disease or condition, including but not limited to, symptomatic cervical spine instability, clinically significant spinal cord compression, or severe cardiac disease that would interfere with study participation, or pose a safety risk, as determined by the Investigator. •Has any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study.
Intervention(s) (n =) and comparator(s) (n =)	**Elosulfase alfa** **Part 1:** Cohort 1 (QW-QW, N=56) received elosulfase alfa weekly given as an intravenous infusion at a dose of 2.0 mg/kg administered over a period of approximately 4 hours in both MOR-004 and Part 1 of MOR-005. Cohort 2 (QOW-QOW, N=59) received elosulfase alfa every other week as an intravenous infusion at a dose of 2.0 mg/kg, with infusions of placebo on alternating weeks, in both MOR-004 and Part 1 of MOR-005. Cohort 3 (placebo-QW, N=29) received placebo in MOR-004 and elosulfase alfa every other week as an intravenous infusion at a dose of 2.0 mg/kg in MOR-005. Cohort 4 (placebo-QOW, N=29) received placebo in MOR-004 and elosulfase alfa every other week as an intravenous infusion at a dose of 2.0 mg/kg administered over a period of approximately 4 hours, with infusions of placebo on alternating weeks in MOR-005 **Part 2** All patients (N=169) received elosulfase alfa weekly given as an intravenous infusion at a dose of 2.0 mg/kg administered over a period of approximately 4 hours.
Duration of follow-up, participants lost to follow-up information	Of the 173 people enrolled into Part 1 of MOR-005, 169 continued into Part 2.

Statistical tests	A repeated measures analysis of covariance (ANCOVA) model was used to compare least square mean changes from baseline at year 1 and 2 of the MOR-005 MPP and MorCAP populations. The model included treatment time point, baseline height, treatment and time point interaction, age group (5–11, 12–18, ≥19 years), baseline 6MWT distance stratification (≤200 m and >200 m), and baseline measurement (for 3MSCT and uKS). Correlations between change in FVC and change in height were estimated using the Pearson correlation coefficient (r).
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline in endurance as measured by the 6MWT in the ITT and MPP populations. The MPP population excludes those who had an orthopaedic surgery during the study or exhibited non-compliance (defined as missing ≥20% of scheduled infusions).
Secondary outcomes (including scoring methods and timings of assessments)	Change from baseline in endurance as measured by the 3-minute stair climb test in the ITT and MPP populations. Percent change from baseline in urine keratan sulphate normalized for urine creatinine in the ITT and MPP populations.
Exploratory efficacy endpoints	Not reported.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; FEV_1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; ITT, intention to treat; MPP, modified per protocol; MPS IVA, mucopolysaccharidosis IVA; MVV, maximum voluntary ventilation; uKS, urine keratan sulphate.

8.2.3 MOR-002 and MOR-100

Table 54. Summary of methods for MOR-002 and MOR-100

Characteristic	Description
Study name	MOR-002/MOR-100
Objective	To evaluate the safety, tolerability and efficacy of elosulfase alfa (BMN 110) in subjects with MPS IVA
Location	Five study centres based in the United Kingdom.

Design	MOR-002 was a Phase 1 and Phase 2 single arm, open-label study designed to assess safety, dose-response using pharmacokinetic and pharmacodynamic measures, and clinical efficacy of elosulfase alfa in subjects between 5 and 18 years of age and diagnosed with MPS IVA. MOR-100 was an open label extension study designed to evaluate the long-term efficacy and safety of elosulfase alfa in MPS IVA. Initially, enrolment was planned for patients involved in any BioMarin-sponsored elosulfase alfa study, apart from MOR-004. Planned recruitment was for up to 100 patients. However, only people completing MOR-002 (N=17) enrolled in MOR-100, with patients involved in other studies in elosulfase alfa offered the option to continue in a protocol-specific extension phase for each study.
Duration of study	Up to 84 weeks for MOR-002 and 3.5 years for MOR-100.
Patient population	Patients with MPS IVA aged between 5 and 18 years.
Sample size	20 for MOR-002 and 100 for MOR-100, but only 17 people enrolled in MOR-100.
Inclusion criteria	MOR-002 •Documented history of reduced GALNS activity relative to the normal range of the laboratory performing the assay, or documented result of molecular genetic testing confirming diagnosis of MPS IVA. •Willing and able to provide written, signed informed consent, or in the case of subjects under the age of 16 years, provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures. •Between 5 and 18 years of age, inclusive. •Sexually active subjects must be willing to use an acceptable method of contraception while participating in the study. •Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study. •Willing to perform all study procedures as physically possible.
Exclusion criteria	MOR-002 •Previous hematopoietic stem cell transplant.

	•Has known hypersensitivity to elosulfase alfa or its excipients. •Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study. •Use of any investigational product or investigational medical device within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments. •Concurrent disease or condition that would interfere with study participation or safety, including, but not limited to, symptomatic cervical spine instability. •Any condition that, in the view of the Principal Investigator, places the subject at high risk of poor treatment compliance or of not completing the study.
Intervention(s) (n =) and comparator(s) (n =)	**MOR-002** Single arm study involving 20 people. Patients received a weekly 4- to 5-hour intravenous infusion of elosulfase alfa in 3 consecutive 12-week dosing intervals, using the following regimen: •Weeks 1–12: 0.1 mg/kg/week; •Weeks 13–24: 1.0 mg/kg/week; •Weeks 25–36: 2.0 mg/kg/week. Those completing the 36-week dose-escalation period had the option to continue drug treatment for an additional 36 to 48 weeks. Patients continuing on treatment after the dose-escalation period received weekly 4- to 5-hour intravenous infusions of elosulfase alfa at a dose of 1.0 mg/kg/week. **MOR-100** Single arm study involving 17 people. A dose of 2.0 mg/kg/week.
Duration of follow-up, participants lost to follow-up information	**MOR-002** Patients were treated for 72 to 84 weeks.

	MOR-100 Additional 192 weeks of treatment to that received in MOR-002.
Statistical tests	For MOR-100, due to the nature of this study, all statistical comparisons were only for descriptive purposes.
Primary outcomes (including scoring methods and timings of assessments)	**MOR-002** Subject incidence of treatment emergent AEs.
Secondary outcomes (including scoring methods and timings of assessments)	**MOR-002** •Change from baseline in 6MWT (time frame: baseline to weeks 12, 24, 36, 48, 72). •Change from baseline in 3MSCT (time frame: baseline to weeks 12, 24, 36, 48, 72). •Percent change from baseline in uKS (time frame: baseline to weeks 12, 24, 36, 48, 72). •Percent change from baseline in MVV (time frame: baseline to weeks 12, 24, 36, 48, 72). •Percent change from baseline in FVC (time frame: baseline to weeks 12, 24, 36, 48, 72). **Additional measures in MOR-100:** •Forced expiratory time. •FEV_1. •FIVC. •Anthropometric measurements (standing height, length, sitting height, and weight). •Skeletal radiographs of lumbar spine and lower extremity. •The MPS Health Assessment Questionnaire. •EuroQoL EQ-5D-5L. •PRO questionnaires.

Exploratory efficacy endpoints	**MOR-100** Changes in biochemical markers of inflammation and bone and cartilage metabolism in subjects with MPS IVA.

Abbreviations: 6MWT, 6-minute walk test; FEV_1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; ITT, intention to treat; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVA, mucopolysaccharidosis IVA; MVV, maximum voluntary ventilation; PRO, patient reported outcomes; uKS, urine keratan sulphate.

8.2.4 MOR-006

Table 55. Summary of methods for MOR-006

Characteristic	Description
Study name	MOR-006
Objective	To evaluate the efficacy and safety of elosulfase alfa in patients with MPS IVA (Morquio A Syndrome) who have limited ambulation.
Location	Three countries (Germany, USA, UK).
Design	Phase 2 open-label, single-arm, multinational study.
Duration of study	Up to 144 weeks.
Patient population	People aged 5 years and over with MPS IVA who have limited ambulation. Limited ambulation defined as an inability to walk ≥30 meters as assessed by the 6MWT performed at the Screening Visit.
Sample size	16 (planned 20).
Inclusion criteria	•Is willing and able to provide written, signed informed consent (or their legally authorized representative) after the nature of the study has been explained and prior to performance of any research-related procedure. Patients who do not meet country and local age requirements for informed consent must be willing and able to provide written assent after the nature of the study has been explained and prior to performance of any research-related procedure.

	•Has documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA. •Is ≥5 years of age. •If sexually active, is willing to use an acceptable method of contraception while participating in the study. •Females of childbearing potential must have a negative pregnancy test at the Screening Visit and be willing to have additional pregnancy tests during the study. •Is willing and able to perform all study procedures as physically possible.
Exclusion criteria	•Is able to walk farther than a specified distance as assessed by the 6MWT. •Has previous HSCT. •Has received previous treatment with elosulfase alfa. •Has a known hypersensitivity to any of the components of elosulfase alfa. •Has had major surgery within 3 months prior to study entry or is planning to have a major surgery during the first 24 weeks of the study. •Has used any other investigational product or investigational medical device within 30 days prior to the Screening Visit or requires any investigational agent prior to completion of all scheduled study assessments. •Is pregnant or breastfeeding at the Screening Visit or planning to become pregnant (self or partner) at any time during the study. •Has a concurrent disease or condition, including but not limited to symptomatic cervical spine instability or severe cardiac disease or complete paralysis due to a spinal cord injury (defined as an inability to move arms and legs), that would interfere with study participation or safety as determined by the Investigator. •Has any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study.
Intervention(s) (n =) and comparator(s) (n =)	Single arm Weekly IV infusions of elosulfase alfa at 2.0 mg/kg/week over a period of approximately 4 hours per infusion for up to 144 weeks.

Duration of follow-up, participants lost to follow-up information	Weekly infusions of 2.0 mg/kg/week elosulfase alfa were administered for 48 consecutive weeks during the initial treatment phase. after which, people could continue into the extension phase of the study for up to an additional 96 weeks of study treatment. 15 patients completed week 48, no patient completed week 144.
Statistical tests	The sample size of the study was not determined by statistical power consideration, as no statistical hypotheses were posed. Statistics were described as descriptive in nature.
Primary outcomes (including scoring methods and timings of assessments)	•To evaluate the effect of 2.0 mg/kg/week elosulfase alfa (as defined by the domains of upper extremity function and dexterity, mobility, pain, and self-care and functional abilities) in a patient population that has limited ambulation, as assessed by: o Percent change from baseline in speed as measured in Functional Dexterity Test (up to 96 weeks); o Change from baseline in strength as assessed by Grip and Pinch Test (up to 96 weeks); o Percent change from baseline in speed as measured in Timed 25-Foot Walk Test (up to 96 weeks).
Secondary outcomes (including scoring methods and timings of assessments)	•Percent increase from baseline in respiratory function tests. •Effect on sleep apnoea •Percent change from baseline in normalized uKS.
Tertiary and exploratory efficacy endpoints	[redacted]

Abbreviations: 6MWT, 6-minute walk test; MPS IVA, mucopolysaccharidosis IVA; uKS, urine keratan sulphate.

8.2.5 MOR-007

Table 56. Summary of methods for MOR-007

Characteristic	Description
Study name	MOR-007
Objective	To evaluate the safety and efficacy of weekly 2.0 mg/kg/wk infusions of elosulfase alfa for up to 208 weeks in paediatric patients diagnosed with MPS IVA, specifically those aged less than 5 years at the time of administration of the first dose of study drug.
Location	Four countries (Italy, Taiwan, USA and UK).
Design	Phase 2 open label, multinational study.
Duration of study	Up to 209 weeks. Initial primary treatment phase of 52 weeks, extension treatment phase of up to an additional 156 weeks, and one week for final study assessments.
Patient population	Patients with MPS-IVA and aged less than 5 years.
Sample size	15
Inclusion criteria	•Less than 5 years of age at the time of the first study drug infusion. •Documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA. •Written informed consent provided by parent or legally authorized representative after the nature of the study has been explained and prior to any research-related procedures.
Exclusion criteria	•Previous hematopoietic stem cell transplant. •Previous treatment with elosulfase alfa.

	•Known hypersensitivity to any of the components of elosulfase alfa. •Major surgery within 3 months prior to study entry or planned major surgery during the 52-week treatment period. •Use of any investigational product or investigational medical device within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments. •Concurrent disease or condition, including but not limited to symptomatic cervical spine instability, clinically significant spinal cord compression, or severe cardiac disease that would interfere with study participation or safety as determined by the Investigator. •Any condition that, in the view of the Investigator, places the subject at high risk of poor treatment compliance or of not completing the study.
Intervention(s) (n =) and comparator(s) (n =)	Single arm study 15 infants received elosulfase alfa weekly given as an intravenous infusion at a dose of 2.0 mg/kg administered over a period of approximately 4 hours.
Duration of follow-up, participants lost to follow-up information	All 15 patients completed the 52 week primary treatment phase and entered the long-term extension. However, no patient completed the planned 156 weeks of long-term follow up.
Statistical tests	Described as descriptive statistics.
Primary outcomes (including scoring methods and timings of assessments)	To evaluate safety and tolerability of Infusions of elosulfase alfa at a dose of 2.0 mg/kg/wk over a 52-week period, and in the longer term.
Secondary outcomes (including scoring methods and timings of assessments)	•Percent change from baseline to in uKS measures. •Change from baseline in normalized growth rate Z-scores.
Exploratory efficacy endpoints	•To characterize the effect of 2.0 mg/kg/week elosulfase alfa on growth plate morphology and bone density in MPS IVA subjects less than 5 years of age at time of first study drug infusion.

	•To characterize the effect of 2.0 mg/kg/week elosulfase alfa on cervical spine and spinal cord morphology in MPS IVA subjects less than 5 years of age at time of first study drug infusion. •Evaluate the effect on: o [redacted]; o [redacted]; o [redacted] o [redacted]; o [redacted]; o [redacted]; o [redacted]; o [redacted]; o [redacted]. •To evaluate phenotype and potential differential treatment responses.

Abbreviations: 6MWT, 6-minute walk test; FEV_1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; ITT, intention to treat; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVA, mucopolysaccharidosis IVA; MVV, maximum voluntary ventilation; PRO, patient reported outcomes, uKS, urine keratan sulphate.

8.2.6 MOR-008

Table 57. Summary of methods for MOR-008

Characteristic	Description
Study name	MOR-008
Objective	To evaluate the safety of a 2.0 mg/kg/week and a 4.0 mg/kg/week dose of elosulfase alfa in patients with MPS IVA for up to 196 weeks.

Location	Four countries (Canada, Germany, USA and UK).
Design	Phase 2 randomised, masked, two-arm multinational pilot study. Randomization was stratified by cohort (A or B). The 15 subjects enrolled in Cohort A were randomized 2:1 to receive 2.0 or 4.0 mg/kg/week elosulfase alfa and performed all study procedures, including the CPET. After completion of enrolment in Cohort A, 10 patients were enrolled in Cohort B and randomized 1:1 to receive 2.0 receive 2.0 or 4.0 mg/kg/week elosulfase alfa; Cohort B subjects performed all study procedures except for CPET.
Duration of study	Planned study duration was up to 196 weeks, including a 3-week Screening, a 27-week primary treatment phase, and up to a 166-week extension phase.
Patient population	Patients at least 7 years of age with MPS IVA who were able to walk at least 200 metres on the 6MWT.
Sample size	25
Inclusion criteria	•Is willing and able to provide written, signed informed consent (or patient's legally authorized representative) after the nature of the study has been explained and prior to performance of any research-related procedure. Also, patients who do not meet country and local age requirements for informed consent must be willing and able to provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to performance of any research-related procedure. •Has documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte N-acetylgalactosamine-6-sulfatase (GALNS) enzyme activity or genetic testing confirming diagnosis of MPS IVA. •Is at least 7 years of age. •Is able to walk ≥ 200 meters as assessed by the 6MWT. •If sexually active, is willing to use an acceptable method of contraception while participating in the study. •If female of childbearing potential, must have a negative pregnancy test at the Screening Visit and be willing to have additional pregnancy tests during the study. •Is willing and able to perform all study procedures, including CPET.

Exclusion criteria	•Inability to perform an exercise test due to limited mobility. •Body weight greater than 95 kg at Screening. •Severe, untreated sleep apnoea as measured during Screening with a home sleep testing device. •Patients with a history of, or current condition of sleep apnoea or sleep disordered breathing under adequate treatment may be enrolled if approved by the medical monitor. •Requirement for supplemental oxygen. •Use of ventilator assistance in the 3 months prior to study entry. •Use of positive airway pressure (continuous positive airway pressure, CPAP, or bilevel airway pressure) for treatment of sleep apnoea or sleep disordered breathing is allowed if settings have been stable for at least 1 month prior to study entry, and is approved by the medical monitor. •Has a concurrent disease or condition, including but not limited to, symptomatic cervical spine instability, clinically significant spinal cord compression, or severe cardiac disease that would interfere with study participation, or pose a safety risk, as determined by the Investigator. •Has previous hematopoietic stem cell transplant. •Has received previous treatment with elosulfase alfa. •Has a known hypersensitivity to elosulfase alfa or its excipients. •Has had major surgery within 3 months prior to study entry or is planning to have a major surgery during the duration of the study. •Use of any other investigational product or investigational medical device within 30 days prior to the beginning of the Screening Period or requires any investigational agent prior to completion of all scheduled study assessments. •Is pregnant or breastfeeding during the Screening Period or planning to become pregnant (self or partner) at any time during the study. •Has a concurrent disease or condition that may interfere with study participation or safety, and/or ability to perform study procedures as determined by the Investigator. •Has any condition that, in the view of the Investigator, poses a safety risk to the patient.

	•Has any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study.
Intervention(s) (n =) and comparator(s) (n =)	Arm 1 (N=15) Elosulfase alfa weekly given as an intravenous infusion at a dose of 2.0 mg/kg administered over a period of approximately 4 hours. Arm 2 (N=10) Elosulfase alfa weekly given as an intravenous infusion at a dose of 4.0 mg/kg administered over a period of approximately 4 hours.
Duration of follow-up, participants lost to follow-up information	Patients who completed the primary treatment phase (27 weeks) enrolled in the extension, during which all patients continued on the same dose of elosulfase alfa up to 52 weeks. After the results of MOR-004 became known, patients receiving the 4.0 mg/kg/week dose transitioned to 2.0 mg/kg/week. 25 patients completed the primary treatment phase of the study and entered the extension phase, but all patients discontinued from the study prior to completion of the extension phase.
Statistical tests	Efficacy analyses include descriptive statistics for all secondary and tertiary efficacy variables. Descriptive statistical summaries of continuous variables include sample size, mean, standard deviation, median, minimum and maximum, and 95% confidence intervals and/or inter-quartile ranges when appropriate. Descriptive summaries of categorical variables included sample size and percent.
Primary outcomes (including scoring methods and timings of assessments)	Treatment phase: safety of 2.0 and 4.0 mg/kg/week elosulfase alfa during the 27-week primary treatment phase of the study. Extension phase: long-term safety of 2.0 mg/kg/week elosulfase alfa.
Secondary outcomes (including scoring methods and timings of assessments)	During the primary treatment period, secondary outcomes were to evaluate the effect of 2.0 and 4.0 mg/kg/week elosulfase alfa on: •Endurance (by 6MWT and 3MSCT); •Overall exercise capacity (by CPET); •RFTs; •MSTs; •Cardiac function;

	•Pain; •uKS levels; •Pharmacokinetic parameters. Secondary outcomes of the extension phase were to evaluate the effect of 2.0 mg/kg/week elosulfase alfa on: •Endurance; •RFTs; •uKS.
Exploratory efficacy endpoints	Tertiary outcomes during the treatment phase were: •To evaluate the effect of 2.0 and 4.0 mg/kg/week elosulfase alfa administered for 24 weeks on growth; •To explore the correlation of the 6MWT and 3MSCT with overall exercise capacity, cardiac function, respiratory function, muscle strength, pain, and plasma and uKS levels; •To obtain a subject's self-rating on his or her experiences associated with the 6MWT, the 3MSCT, and with breathing; •To evaluate the effect of 2.0 and 4.0 mg/kg/week elosulfase alfa administered for 26 weeks on biochemical markers of bone and cartilage metabolism. Tertiary objectives of the extension phase of the study were: •To evaluate the effect of 2.0 mg/kg/week elosulfase alfa on growth; •To explore the correlation of the 6MWT and 3MSCT with respiratory function and uKS levels; •To evaluate the effect of 2.0 mg/kg/week elosulfase alfa on cardiac function; •To evaluate the effect of 2.0 mg/kg/week elosulfase alfa on biochemical markers of bone and cartilage metabolism.

Abbreviations: 6MWT, 6-minute walk test; CPET, cardiopulmonary exercise testing; FEV_1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; ITT, intention to treat; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVA, mucopolysaccharidosis IVA; MVV, maximum voluntary ventilation; PRO, patient reported outcomes; uKS, urine keratan sulphate.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 1 April** using the below comments table.

All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

1.2 Overview of key model outcomes (p.17)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P.17: typo mistake in below bullet point *'•Increasing patients' recovery time from surgery'*	Change to: '*Decreasing patients' recovery time from surgery*'		The ERG thanks the company and has amended the text as suggested.

Issue 7: Company's modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Based on further correlation analysis conducted on the MAA data and broader evidence, the Company considers that this paragraph in the report puts too much focus/emphasis on the correlation between respiratory measures (FVC) and EQ-5D/HRQoL, while other measures such as endurance (6MWT) and WC states have shown a stronger correlation with EQ-5D. Page 22: *'The ERG also concluded that there is evidence to support a strong correlation between […] patients'*	The relevant evidence does not support a strong correlation between the respiratory function (FVC) and EQ-5D, when compared to other measures such as endurance (6MWT) and WC states. Whilst the Lampe et al. paper does show a correlation of FVC and EQ-5D, it is in a small population of German patients and is not consistent with other evidence in larger datasets in MPS IVA and especially with the English MAA dataset, which is most representative of the population in scope. In addition, to support this assumption in the clarification responses, the Company provided further evidence of very poor correlation between FVC and EQ-5D based on a correlation analysis using the MAA data (pages	A stronger correlation was found between 6MWT, WC status and EQ-5D-5L/HRQoL, therefore supporting the Company's modelling assumptions. The focus on the small German cohort study in the ERG report is not reflective of the English patient population.	Not a factual error.

respiratory measures (FVC) with patient's EQ-5D-5L/HRQoL.'	73-74 – ID1643 clarification letter from ERG 150121 [ACIC]_v4_22022021). Furthermore, in other musculoskeletal conditions such as DMD, it was also shown that many parameters of HRQoL correlate poorly to the respiratory function (Kolher et al., 2005). The Company would therefore suggest amending this paragraph to better acknowledge these correlation differences and the stronger relevance of the MAA dataset (vs Lampe paper) that have justified the choice of measures of HRQoL for the modelling approach.		

Issue 8: Estimation of WC dependency in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The Company believes that the issue raised below has been addressed in the revised model and results based on the suggested transition probabilities by the ERG in the clarification document. Page 23: *'The ERG disagrees with the company's method for estimating transition probabilities across the WC states in the model.* *Given the availability of annual WC use data, it is unclear to the*	During the consultancy period, based on ERG's recommendation, the Company provided analysis where yearly transition probabilities (page 65 - ID1643 clarification letter from ERG 150121 [ACIC]_v4_22022021) were included in the model. In responses to B1, B4, and B5 questions to ERG, the Company provided yearly transition probabilities and updated the model accordingly for the first 10 years. For ex-trial patients, the QALY gain was [redacted] QALYs (vs [redacted] earlier) and the ICER was £[redacted]. For treatment-naïve patients. the QALY gain went down from [redacted] QALYs to [redacted] QALYs, and the ICER was £[redacted].	The report should reflect the results based on revised transition probabilities suggested by the ERG as part of the response on 22nd February (ID1643 clarification letter from ERG 150121 [ACIC]_v4_22022021).	Not a factual error. For clarification, the ERG notes that the company's base case has not changed as a result of the clarification stage, therefore, the issue described in page 23 and page 112 of the ERG report is still applicable. Furthermore, the ERG notes that the report includes a recommendation on how to use the annual data in the model once the clinical data have been re-analysed.

ERG why the data used to model transitions in the first year of the model was based on the WC change from baseline to 72 weeks in the MAA dataset and from baseline to 2 years in the MOR-001 study, respectively. *The ERG has several concerns around the estimates used to derive the increase in WC dependency for SoC patients in the following years of the model, through the use of 6MWT and FVC outcomes.'*	Therefore, the Company proposes to amend the report in order to account for the submitted clarification response based on the updated transition probabilities in the first 10 years.		

Issue 10: Estimation of quality of life in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The Company disagrees that older utilities from the HST2 should be used, as the MAA data is the most representative and recent data source from treated English patients. Page 25: *'The ERG recommends that the company uses the same utilities values from the HST2; that all WC states have the same utility in both treatment arms, and utility increments associated with*	Based on recommendation from the ERG, data from the MAA treatment-naïve patients represent the best source of real-world data from an English cohort, therefore supporting the Company's use of utility values in the model derived from the MAA data.	MAA treatment naïve patents represents the best source of data for patients in England (ERG report page 87). *'Of the included ESA studies in the company's SLR, the ERG considers the QW-QW subgroup of MOR-005, the MAA to be of the most relevance to the NICE final scope. This is because the MAA reflects treatment with ESA of UK patients since the NICE appraisal*	Not a factual error.

gains in the 6MWT and FVC outcomes observed for ESA are estimated; and finally, that the FVC and 6MWT increments used are those underpinning the treatment effectiveness analysis and the clinical data used in the model.'		*of ESA in HST2 and the QW-QW subgroup of MOR-005 comprises patients who have received the recommended EU licensed dose of ESA from the start of treatment.'*	

(please cut and paste further tables as necessary)

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**ERG response**
ID1643 elosulfase alfa Factual accuracy check ACIC check form_vf Section 4.2.4.1, page 78, Table 17, row on MAA	Patient number should be marked as AIC.	N=[redacted]	The ERG thanks the company and has marked the text as suggested.

ID1643 elosulfase alfa Factual accuracy check ACIC check form_vf Page 86, Table 27	Patient number and outcomes should be marked AIC.	Table 27. ERG's exploratory complete case analysis for 6MWT and FVC in MAA ERT-Naïve patients (3-year timeframe) 	The ERG thanks the company and has marked the text as suggested.
ID1643 elosulfase alfa Factual accuracy check ACIC	MAA patient number requires AIC marking.	'As a response, the company conducted various regression analyses using the MAA data ([redacted] patients) to investigate how age; weight; urinary keratan sulphate; the 6-minute walking test (6MWT).'	The ERG thanks the company and has marked the text as suggested.

check form_vf Section 4.2.4.1, page 98, 3rd paragraph			
ID1643 elosulfase alfa Factual accuracy check ACIC check form_vf Section 4.2.4.1, page 101, Table 30	MAA patient number and baseline FVC and 6MWT across WC states require AIC marking.	Table 30. Baseline FVC and 6MWT in MAA across WC states – ERG's complete case analysis 	The ERG thanks the company and has marked the text as suggested.
ID1643 elosulfase alfa Factual accuracy check	Company's base case ICER should be marked CIC.	For example, if all ESA patients in the model were assumed to be mild progressers instead of stable patients, which in the model meant that ESA patients would progress 50% less than SoC patients (but still had some progression) the company's base case ICER would increase from [redacted] to [redacted].	The ERG has marked the text as suggested.

ACIC check form_vf Page 114, 2nd paragraph			
ID1643 elosulfase alfa Factual accuracy check ACIC check form_vf Section 4.2.8, page 127, Table 37	Base case model utility values based on MAA dataset require CIC marking.	Table 37. Model utility values 	The ERG has marked the text as suggested.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the evaluation committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the evaluation committee meeting.

Deadline for comments **5pm on Friday 27th August 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form:

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Anne-Helene Monsimier
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank).	BioMarin International Limited and BioMarin (UK) Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Lack of robust comparative data for elosulfase alfa compared to standard of care and the heterogeneity of mucopolysaccharidosis type IVA.	**YES**	• The Company acknowledges that mucopolysaccharidosis type IVa is multi-systemic, heterogeneous condition. • In response to the Evidence Review Group requests at clarification stage, the Company provided a propensity score matching report where Managed Access Agreement patients were matched to MOR-001 patients, with baseline age, 6-minute walking test, forced expiratory volume in 1 second, forced vital capacity, urinary keratan sulfate, weight, and sex used as covariates. • 6-minute walking test as an outcome is consistent with the primary endpoint in the clinical programmes as a measure of endurance. • The results at Years 1, 2, and 3 post-treatment demonstrated that compared with no treatment, patients receiving elosulfase alfa had an improvement in 6-minute walking test of between [redacted] metres. • The Company has performed further analysis and used all available 6-minute walking test data for patients with complete cases at Years 1 and 2 to present a comparative analysis of Managed Access Agreement versus MOR-001 patients. Please see Section 2.3 in the submission report document.

<table>
<tr>
<td>Key issue 2: Use of elosulfase alfa treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation in some of the ex-trial ‘managed access agreement’ patients.</td>
<td>YES</td>
<td>

The Company acknowledges that MOR-004 is a randomised, double-blind, placebo-controlled trial conducted over 24 weeks, evaluating two dosing cohorts (2 mg/kg/week and 2 mg/kg/every other week) with sample sizes [redacted] and [redacted] in each cohort, respectively.
The change from baseline in 6-minute walking test was greater in the once weekly group compared with every other week and placebo groups:

<table>
<tr><th>Change from baseline in 6MWT (metres)</th><th>Placebo (n= [redacted])</th><th>ESA-2 mg/kg/QOW (n= [redacted])</th><th>ESA-2 mg/kg/QW (n= [redacted])</th></tr>
<tr><td>Mean (standard deviation)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

The Company has presented the pooled once weekly and every other week pooled results; however, these can be considered a conservative assessment of treatment effect on 6-minute walking test.
There were [redacted] patients from trial MOR-004 who continued to the Managed Access Agreement stage. However, the limited patient number (n=[redacted]) means any delineation of MOR-004 into two dosing regimens will substantially limit the analysis requested (propensity score matching of Managed Access Agreement versus MOR-001 patients)
The new complete case analysis which the Company has produced includes results for all Managed Access Agreement patients in the base-case. The Company has also included results (as a sensitivity analysis) of treatment-naïve patients (i.e., patients who started treatment in the Managed Access Agreement). The results demonstrated that there was a greater treatment effect observed in treatment-naïve patients compared with all Managed Access Agreement patients. Please see Section 2.3 and 3.2 in the submission report document.

</td>
</tr>
</table>

Key issue 3: Absence of a systematic literature review to identify studies for standard of care.	**YES**	• A clinical systematic literature review was conducted by the Company in November 2019, with an updated search in November 2020, to identify published, or, as yet, unpublished randomised, non-randomised, or single-arm studies/case series conducted with elosulfase alfa in mucopolysaccharidosis type IVa. • Due to time constraints, a *de novo* full systematic literature review could not be performed for this submission. Please note that if the Company had conducted a full *de novo* systematic literature review, the Company acknowledges that these time constraints would have prohibited any new studies/data identified from being incorporated into the model as this would have required a fundamental change to the model structure. • In the absence of a full *de novo* systematic literature review, the approach taken was to update the original systematic literature review; this was updated in June 2021. The eligibility criteria were amended to allow the identification of studies published post-2019 relating to standard of care for mucopolysaccharidosis type IVa other than enzyme replacement therapy. Of the studies identified in the June 2021 update, it is the Company's assessment that these did not provide any further robust/quality data above those already included in the model. Please see Section 2.2 in the submission report document.

Key issue 4: Clinical heterogeneity in the clinical analyses and inappropriate methods for handling of missing data.	**YES**	• The model structure has not changed from the original submission in 2015, which was the basis for decision-making at that time, and has only been updated with new data from the Managed Access Agreement. • The Evidence Review Group report acknowledges that Managed Access Agreement and MOR-001 represents the best source of data for patients receiving treatment and for treatment-naïve patients. • It was not possible to conduct a new propensity score matching analysis due to the need to re-analyse all Managed Access Agreement data and MOR-001 data and the time constraints this task imposed; however, the MorCAP1 population was used, which has less heterogeneity than the overall MOR-001 population, as it applied the inclusion criteria for the MAA to the MOR-001 population in order to create a pseudo-comparator arm which similar characteristics to the MAA patients (age ≥ 5, 6MWT at baseline of ≥30m and < 325m). • A complete case analysis for patients with data available at Years 1 and 2 was conducted in line with the Evidence Review Group's request. Please see Section 2.3 in the submission report document.
Key issue 5: Use of inconsistent timepoints within and between studies for assessment of clinical outcome data.	**YES**	• This has been addressed by the reassignment of timepoints, as agreed with the Evidence Review Group, using the methods described in the submission report document. Please see Section 2.3 in the submission report document.

Key issue 6: Clinical data used in the model: The data included in the economic model are unfit for decision making.	**YES**	• This request is contrary to the discussion and agreement the Company had with the National Institute for Health and Care Excellence and National Health Service England. The National Institute for Health and Care Excellence decision in 2015 was based upon the submission made in 2015, with the understanding that at the expiry of the Managed Access Agreement, the submission will be populated with new Managed Access Agreement data. • Accordingly, the current submission has been made retaining the structural integrity of the original submission, with new Managed Access Agreement data included. • As acknowledged in the Evidence Review Group report, Managed Access Agreement data represents the best data source for patients on treatment in England. Furthermore, the MorCAP1 subpopulation of MOR-001 provides the best source of data for patients not receiving treatment. • The analyses were based on a new flat data file which was generated by re-analysing the original MAA database, keeping an audit log of all data cleaning conducted, and addressing the ERG's concerns surrounding timepoints used in the MOR-001 study.

Key issue 7: Modelling approach: The use of a wheelchair-based model is unlikely to capture the impact of elosulfase alfa on patients' disease and the thresholds for change in wheelchair use in the model are contradictory to the underlying clinical data.	**NO**	• As wheelchair use is strongly associated with quality of life, the original structure of the model, submitted in 2015, has been retained for this submission with inputs revised to reflect the new complete case analysis of Managed Access Agreement data. • The original submission in 2015 was based on wheelchair status which was agreed with clinical experts as the best proxy of patient functioning and quality of life. • The Company engaged with clinical experts at two advisory boards in December 2020 and January 2021 where the clinical experts could not suggest an alternative to the original assumptions of wheelchair status driving patients' functioning and quality of life. • The underlying assumptions of transition between wheelchair states is underpinned by the new Managed Access Agreement data (which has been acknowledged to be the best data source) reflecting patients in England. • These wheelchair states were collected as part of the Managed Access Agreement (Mucopolysaccharidosis-Health Assessment Questionnaire questions 33 and 33a). • As part of this analysis, the relationship between respiratory function (forced vital capacity) and quality of life (European Quality of Life-Five Dimension) was investigated; however, no such correlation was identified. This is demonstrated in the statistical methods in section 2.3.2.9 of the updated resubmission report. • The relevant evidence does not support a strong correlation between respiratory function (forced vital capacity) and quality of life (European Quality of Life-Five Dimension), when compared to other measures such as endurance (6-minute walking test) and wheelchair status. While the Lampe et

		al. 2015 article does show a correlation of forced vital capacity and European Quality of Life-Five Dimension, it is in a small population of German patients and is not consistent with other evidence in larger datasets in mucopolysaccharidosis type IVa and especially with the English Market Access Agreement dataset, which is most representative of the population in scope. In addition, to support this assumption in the clarification responses, the Company provided further evidence of very poor correlation between forced vital capacity and European Quality of Life-Five Dimension based on a correlation analysis using the Market Access Agreement data.

Key issue 8: Estimation of wheelchair dependency in the model: Given the availability of annual wheelchair use data, it is unclear to the ERG why these were not used by the company. The ERG disagrees with the company's assumptions of constant decline in the standard of care arm and the company's assumption that after year 1 in the model, only 0.01% of elosulfase alfa patients progress to the next (more dependent) wheelchair state in the model.	**YES**	• Wheelchair status shifts have been updated using a complete case approach as described in the statistical methods. Please see Section 2.3 in the submission report document • Implementation of additional transition matrices would have required significant structural changes to the model which could not be implemented due to time constraints • At the consultation stage, the Company provided a scenario analysis with yearly transitions imputed for the first 10 years of the Markov cycles. • For treatment-naïve patients the incremental cost-effectiveness ratio was [redacted] and [redacted] for ex-trial patients. • The Company response to consultation demonstrated that wheelchair use is strongly associated with European Quality of Life-Five Dimension (r=-0.3543, n=181, p<0.5); patients who reported more wheelchair use therefore have a lower utility score which justifies the health states pertaining to wheelchair use. • Pulmonary function varies widely within, and between, patients and does not correlate well with the Mucopolysaccharidosis-Health Assessment Questionnaire mobility domain. Changes in entry and exit from the health states is currently driven by the 6-muinute walking test. • Endurance (6-minute walking test) and age are significant predictors of wheelchair use. The model's current structure in the base-case is therefore the most reasonable approach based on available evidence.

Key issue 9: Mortality - The company's approach to estimating mortality is overestimating survival in the model.	**YES**	• Scenario analysis was performed reducing the relative risk which resulted in little impact on the incremental cost-effectiveness ratio. • Changing the relative risk from 1.12 to 1.15, as recommended by the Evidence Review Group (based on the Neas and Schwartz, 1988 study) had no impact on the incremental cost-effectiveness ratio. • Adjusting the relative risk to be the same for patients receiving treatment and those not receiving treatment resulted in the incremental cost-effectiveness ratio increasing from [redacted] to [redacted].
Key issue 10: Estimation of quality of life in the model: The company's justification for having treatment-specific utility values by wheelchair category is inconsistent with the company's justification for having a wheelchair-based model and it double counts the benefits associated with elosulfase alfa.	**YES**	• There was an agreement in 2015 to add increment to account for additional benefits in quality of life (e.g., eyesight, etc.) beyond wheelchair status. • However, for this submission the utility values were kept the same in both arms. These utility values come from the new complete case analysis of the Managed Access Agreement data. • The resulting new ICER is presented in section 3.2 in the submission report document.
Key issue 11: Elosulfase alfa costs - The company underestimated the treatment costs in the analysis.	**YES**	• Patient weights have been recalculated based on the complete case analysis and stratified based on all patient populations available. • The 20% discount has been removed from the base case results.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
• **Additional issue 1: N/A**	• Please indicate the section(s) of the ERG report that discuss this issue	• YES/NO	• Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

The Company confirm that no additional issues were raised in the Evidence Review Group report or by the National Institute for Health and Care Excellence that required to be addressed.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
• **Key issue 1:** Lack of robust comparative data for elosulfase alfa compared to standard of care and the heterogeneity of mucopolysaccharidosis type IVa.	• The original submission was based on the analysis of all patients in the Managed Access Agreement for whom data was available.	• Complete case analysis.	• New QALY gain and ICER: [redacted] & [redacted]. • Original QALY gain and ICER: [redacted] and [redacted].
• **Key issue 2:** Use of elosulfase alfa treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation in some of the ex-trial 'Managed Access Agreement' patients.	• The original submission was based on the analysis of all patients in Managed Access Agreement for whom data was available.	• Complete case analysis of treatment-naive patients who started treatment in the Managed Access Agreement.	• New QALY gain and ICER: [redacted] & [redacted]. • This analysis was not produced in original submission.

• **Key issue 6:** Clinical data used in the model: The data included in the economic model are unfit for decision making.	• The original submission was based on the analysis of all patients in Managed Access Agreement for whom data was available.	• Complete case analysis.	• New QALY gain and ICER: [redacted] & [redacted]. • Original QALY gain and ICER: [redacted] and [redacted].
• **Key issue 10:** Estimation of quality of life in the model: The company's justification for having treatment-specific utility values by wheelchair category is inconsistent with the company's justification for having a wheelchair-based model and it double counts the benefits associated with elosulfase alfa.	• There was an agreement in 2015 to add increment to account for additional benefits in quality of life (e.g., eyesight, etc.) beyond wheelchair status.	• For this submission the utility values were kept the same in both arms. These utility values come from the new complete case analysis of the Managed Access Agreement.	• New QALY gain and ICER: [redacted] & [redacted]. • Original QALY gain and ICER: [redacted] and [redacted].
• The Company's preferred base-case following technical engagement.	• Incremental QALYs: [redacted].	• Incremental costs: [redacted].	• New QALY gain and ICER: [redacted] & [redacted]. • Original QALY gain and ICER: [redacted] and [redacted].

Vimizim NICE HST Resubmission Report

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

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Abbreviations

6MWT	6-minute walking test
BiPAP	Bilevel positive airway pressure
BMJ	British Medical Journal
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
ECG	Electrocardiogram
EQ-5D	European Quality of Life-Five Dimension
EQ-5D-5L	European Quality of Life-Five Dimension-Five Level
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
G-BA	Gemeinsame Bundesausschuss
HAS	Haute Autorité de santé
HST	Highly Specialised Technologies
ICER	Incremental cost-effectiveness ratio
MA	Meta-analysis
MAA	Managed Access Agreement
MPS IVa	Mucopolysaccharidosis type IVa
MPS-HAQ	Mucopolysaccharidosis Health Assessment Questionnaire
NICE	National Institute for Health and Care Excellence
PSM	Propensity score matching
RCT	Randomised controlled trial
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SSIEM	Society for the Study of Inborn Errors in Metabolism
uKS	Urinary keratan sulfate

Glossary

Ex-trial	Patients who started in the MAA following involvement in the clinical trial programme
MAA	Patients enrolled in the MAA, including both ex-trial patients and treatment-naïve patients
MOR-001	Natural history study that included patients not on active treatment i.e., best supportive care
Treatment-naive	Patients who were not included in the clinical trial programme and who started in the MAA post-2015

1 Executive summary

1.1 Disease background

Mucopolysaccharidosis type IVa (MPS IVa) is a genetic metabolic disorder in which patients inherit mutations in both copies of the N-acetylgalactosamine-6-sulfate sulfatase (GALNS) gene. Given the wide genetic variability underlying MPS IVa, the clinical manifestation of the disease is highly heterogenous across patients. Due to disease heterogeneity, patients exhibit a variety of symptoms with varying disease severity leading to substantial differences in response to treatment.

1.2 Clinical systematic literature review

To support the NICE HST submission for elosulfase alfa in MPS Iva, a clinical SLR was conducted to identify published, or, as yet unpublished randomised, non-randomised or single arm studies/case series conducted with elosulfase alfa in MPS IVa. The original SLR conducted in November 2019 was updated in June 2021, with a total of 11 studies identified that reported on the incidence and/or longitudinal outcomes in patients with MPS IVa, including respiratory, cardiac, correction of spinal lesions, orthopaedic, ophthalmology, sleep disruption, anthropomorphic features, otorhinolaryngology, and functional outcomes across the studies.

1.3 Efficacy data

A flat file (i.e., a single file containing all data across all patients and relevant outcomes) was required to perform statistical analyses. After consultation with NICE and the ERG during technical engagement, a new flat file was generated using the original BioMarin Microsoft Access database, with data cleaning and interpretation of results recorded. Numerical differences were observed from baseline to Years 1 and 2 for the clinical outcomes of interest for patients with MPS IVa receiving elosulfase alfa; however, subsequent analyses demonstrated these differences were not statistically significant which was likely attributable to the low patient numbers available due to the complete case analysis approach that was taken.

1.4 Elosulfase alfa value story and patient case studies

When combined with the rarity of the disease, heterogeneity means it is challenging to draw conclusions regarding the optimal management of patients, and there is a need to draw on expert clinical experience to develop guidance. Patient cases provided specific, relevant examples of treatment outcomes that could not be captured in the trial data but are of particular importance to patients' quality of life. Reports from clinicians indicate that improvement is seen when observing patients on an individual basis, including improvements in their ability to carry out simple everyday tasks that may be missed during clinical trials. Expert clinical opinion was that in clinical practice, compared with before treatment or no treatment, patients with MPS IVa receiving elosulfase alfa had a sustained improvement in 6MWT over time, an improvement and stabilisation of lung function, sustained growth, a reduced dependency on wheelchair use, increased independent functioning, a reduction in pain medication/analgesic use, and an increase in the number of surgeries being performed due to patients being better candidates for surgery as a result of receiving elosulfase alfa.

1.5 Economic results

Following implementation of changes as per the ERG's requests, the ICERs were similar to the base case ICERs calculated for the original submission for the undiscounted results (undiscounted original ICER: £[redacted]; undiscounted updated ICER: £[redacted]) and were approximately [redacted]% higher for the discounted results (original ICER: £[redacted]; discounted updated ICER; £[redacted]). The main driver of the economic results (excluding discount rates) was the probability of transitioning to the wheelchair-dependent health state.

2 Clinical section

2.1 Clinical systematic literature review – November 2019

To support the NICE HST submission for elosulfase alfa in MPS IVa a clinical SLR was conducted to identify published, or, as yet unpublished randomised, non-randomised or single arm studies/case series conducted with elosulfase alfa in MPS IVa. The original SLR was conducted in November 2019 and updated in June 2021.

2.1.1 Eligibility criteria

The inclusion and exclusion criteria for the SLR are presented in Table 1.

Table 1: PICOS eligibility criteria for the clinical SLR

Characteristic	Inclusion criteria	Exclusion criteria
Population	• MPS IVa (Morquio syndrome) • Any age group (children or adults)	• Population not of interest e.g. non-human data or mixed patient populations (e.g. MPS IVa and other MPS types without MPS IVa data reported separately) o Where non-human and human data is reported the study will be included if the human data is of relevance o Papers where 80% of the population is of interest will be included, or papers where subgroup data with the population of interest are reported separately
Mixed populations	• Data reported for paediatric and adult populations (mixed data) is also eligible. Where reported separately, the mixed and separate population data will be extracted	• <80% of enrolled patients are of the population of interest and data for population of interest not reported separately
Interventions/ comparators	• In MPS IVa, at least one treatment arm has a licensed dose of ERT e.g. ESA 2mg/kg of body weight given once per week by i.v. infusion over at least 4 hours	• Treatment in MPS IVa not of interest (e.g. HSCT, gene therapy, symptomatic treatment (physiotherapy / surgery) • No comparator of interest or unlicensed dose for treatment of interest (e.g. every other week dosing) without a licensed treatment arm of interest
Outcomes	• Study reports any of the following outcomes of interest: o Endurance assessments (6MWT, T25FW/MSFC, stair climb test, pinch/grip test, functional dexterity test o Pain o Fatigue o Psychological assessments o Urinary KS	• No outcome of interest

Characteristic	Inclusion criteria	Exclusion criteria
	o Heart function o Lung function o Survival o Audiometry tests o Sleep apnoea o Corneal clouding o Muscle strength o HRQoL: MPS-HAQ and ADL (listed only)	
Study design	• RCTs, non-RCTs, single arm/case series SLRs/NMAs*	• Study design not of interest, e.g.: o Case reports o n=1 before-and-after studies o PK/PD study only o Non-systematic reviews o Observational data o Phase 1 only studies o Retrospective studies o Post-hoc pooled analyses o Pilot studies o Economic analyses or budget impact analyses o In vitro studies or animal studies
Date limits	• Unlimited	• N/A
Child abstract	• Sub-study abstract with unique data that could be reffered to	• Child abstract or sub-study with no unique data
Publication type	• Errata • Original articles • Technology appraisal documents, if original source not available elsewhere	• Publication type not of interest, e.g.: o Editorials o Commentaries o Letters o Notes o Protocol-only articles.
Languages	• Electronic searching not limited to the English language • Any non-English language articles deemed relevant were discussed to decide on final inclusion. For non-English language articles that were included, these were translated and/or relevant information extracted +	• N/A

* Relevant SLRs and meta-analyses were kept in at first pass for cross-referencing/bibliography checking purposes but were excluded at second pass.
+ Language capabilities include English, Czech, Danish, French, German, Hungarian, Italian, Polish, Portuguese and Spanish.
Abbreviations: ADL, activities of daily living; ERT, enzyme replacement therapy; ESA, elosulfase alfa; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplantation; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVa, mucopolysaccharidosis type IVa; MSFC, multiple sclerosis functional composite; 6MWT, 6-minute walk test; NMA, network meta-analysis; SLR, systematic literature review; T25FW, timed 25-foot walk test.

2.1.2 Information sources

2.1.2.1 Databases

The databases searched for the clinical SLR are presented in Table 2 and Table 3.

Table 2: Electronic databases searched as part of the clinical SLR

Database	Platform	Span of search	Date searched
Embase	Embase.com	Database inception (1974) to date of search	11-Oct-2019
Medline	Embase.com	Database inception (1966) to date of search	11-Oct-2019
MEDLINE In-Process and e-publications ahead-of-print	PubMed interface http://www.ncbi.nlm.nih.gov/pubmed/http://www.ncbi.nlm.nih.gov/pubmed/	From inception to the day prior to the searches	11-Oct-2019
Cochrane library CDSR	http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception (1966) to Issue 9 of 12, September 2019 (database updated monthly)	11-Dec-2019
Cochrane library CENTRAL	http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception (1966) to Issue 9 of 12, September 2019 (CENTRAL is updated monthly)	11-Dec-2019

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials.

Table 3: CRD database and registries searched as part of the clinical SLR

Database	Platform	Span of search	Search terms	Date searched	Results
DARE, NHS EED and HTAD, now hosted by CRD	https://www.crd.york.ac.uk/CRDWeb/	From database inception (1966) to Issue 2 of 4, April 2015 (database is now closed as of 31st March 2015)	Any field: mucopolysaccharidosis IVa	18-Dec-2019	7
US NIH registry & results database	https://clinicaltrials.gov	Unlimited	(morquio OR MPS IV OR MPS IV A OR MPS IVa OR mucopolysaccharidosis IV OR mucopolysaccharidosis IVa) [DISEASE] All other settings unlimited	14-Jan-2020	180

Abbreviations: CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; HTAD, Health Technology Assessment Database; NHS EED, National Health Service Economic Evaluation Database; MPS, mucopolysaccharidosis; NIH, National institutes of Health; US, United States.

2.1.3 Conference abstracts

Relevant clinical conferences searched for the preceding two years are presented in Table 4.

Table 4: Conferences searched as part of the clinical SLR

Research meeting	Source	Search terms (hits)
Program and Abstracts WORLD Symposium 2019 15th Annual Research Meeting	• Molecular Genetics and Metabolism 2019, Volume 126, Issue 2, Pages S1-S172	• MPS IVa (5) • Mucopolysaccharidosis (41) • Morquio (11)
Program and Abstracts WORLD Symposium 2018	• Molecular Genetics and Metabolism 2018, Volume 123, Issue 2, Pages S15+	• MPS IVa (3) • Mucopolysaccharidosis (44) • Morquio (6)
SSIEM 2019, Rotterdam	• SSIEM 2019 abstract book	• MPS IVa (21) • Mucopolysaccharidosis (71) • Morquio (36)
SSIEM 2018, Athens	• SSIEM 2018 JIMD (2018) 41 (Suppl 1):S1-S36 (titles) • JIMD (2018) 41 (Suppl 1):S37-S219 (abstracts), via Deepdyve.com	• MPS IVa (6) • Mucopolysaccharidosis (37) • Morquio (0)

Abbreviations: JIMD, Journal of Inherited Metabolic Disease; MPS, mucopolysaccharidosis; SSIEM, Society for the Study of Inborn Errors of Metabolism.

2.1.3.1 Hand-searching

In addition to the data sources described above, hand-searches were also conducted to ensure completeness. The following hand-searches were conducted:

- Bibliographic reference lists of included papers
- Bibliographic reference lists of relevant SLRs and meta-analyses from 2018 onwards identified during screening
- Unpublished data known to the manufacturer up to September 2019
- Unpublished data reported on clinicaltrials.gov
- Google hand-searching – for full texts of relevant abstract-only data from electronic screening
- NICE, SMC, HAS, G-BA websites – for manufacturer submission/appraisal data (technology appraisals, ERG evaluation reports, Committee Papers, etc.)

2.1.4 Search strategy

The search strings combine MPS IVa terms AND study design terms; conference reviews, chapters, editorials, letters, notes, and case reports are then excluded from the string. The usual method for excluding non-human studies was not used, as it has been noted that articles can be wrongly excluded if incorrectly indexed as non-human. Non-human articles were therefore excluded with a specific bespoke filter identifying rodent terms in the title.

2.1.4.1 Embase/Medline search string

The search string for Embase/Medline is presented in Table 5. Searching Embase and Medline together via Embase.com excludes any duplicates between Embase and Medline. Randomised controlled trials (RCTs) were identified in Embase using the Embase RCT search strategy, amended to Embase.com format (see line #2 below).

To identify non-RCTs, extension studies, registry data, case-control studies and case-series, a bespoke string was developed based on the British Medical Journal's (BMJ's) search filter to identify cohort studies, case-control studies, and case-series. The adapted filter included the BMJ filter, amended to Embase.com format (line #3), as well as additional terms for extension studies and registry data (lines #4 and #5).

Table 5: Search string for Embase/Medline via Embase.com

No.	Query	Results
#1	'morquio syndrome'/exp OR morquio*:de,ab,ti OR morqio*:de,ab,ti OR morkio*:de,ab,ti OR brailsford*:de,ab,ti OR keratosulfaturia*:de,ab,ti OR osteochondrodystrophia*:de,ab,ti OR galns*:de,ab,ti OR 'n acetylgalactosamine 6 sulfatase':de,ab,ti OR 'n acetylgalactosamine 6 sulfate':de,ab,ti OR 'n acetyl d galactosamine 6 sulfate 6 sulfohydrolase':de,ab,ti OR 'n acetyl d galactosamine 6 sulphate 6 sulfohydrolase':de,ab,ti OR 'n acetylgalactosamine 6 sulphate sulfatase':de,ab,ti OR mpsiv*:de,ab,ti OR 'mps iv':de,ab,ti OR 'mps iva':de,ab,ti OR 'iv mps':de,ab,ti OR 'iva mps':de,ab,ti OR mps4*:de,ab,ti OR 'mps 4':de,ab,ti OR 'mps 4a':de,ab,ti OR '4 mps':de,ab,ti OR '4a mps':de,ab,ti OR ((('typ? 4' OR 'typ? iv' OR typ?4 OR typ?iv OR 'typ? 4a' OR 'typ? iva' OR typ?4a OR typ?iva) NEAR/5 (mps* OR muco* OR muko*)):de,ab,ti) OR ((typ* NEAR/3 (four OR '4' OR '4a' OR iv OR iva) NEAR/5 (mps* OR muco* OR muko*)):de,ab,ti) OR ((familial NEAR/3 osseous NEAR/3 dystrophy):de,ab,ti) OR ((kerato NEAR/3 sulfaturia):de,ab,ti) OR (((mucopolysaccharidos* OR mucopolysacharidos* OR mukopolysaccharidos*OR 'muco polysaccharidosis' OR 'muco polysaccharidoses') NEAR/7 (four OR '4' OR '4a' OR iv OR iva OR 'typeiv' OR 'type4')):de,ab,ti)	3069
#2	'crossover procedure':de OR 'double blind procedure':de OR 'randomized controlled trial':de OR 'single blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEAR/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR (((doubl* OR singl*) NEAR/1 blind):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2476512
#3	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'case control study'/exp OR 'case study'/exp OR cohort*:de,ab,ti OR (case*:de,ab,ti AND control*:de,ab,ti) OR (case*:de,ab,ti AND series:de,ab,ti	3864384
#4	nonrandomi$ed:ab,ti OR 'non randomi$ed':ab,ti OR (((controlled OR extension) NEAR/3 (trial* OR study OR studies OR phase)):ab,ti)	492932
#5	'register'/exp OR 'disease registry'/exp OR register:ab,ti OR registry:ab,ti	272219
#6	#2 OR #3 OR #4 OR #5	5974188
#7	#1 AND #6	526
#8	'systematic review'/exp OR 'meta analysis'/exp OR 'comparative effectiveness'/exp OR metaanalysis:ab,ti OR 'meta analysis':ab,ti OR 'meta regression':ab,ti OR 'adjusted indirect comparison':ab,ti OR ((systematic* NEAR/3 review*):ab,ti) OR (((mixed OR indirect) NEAR/3 treatment*NEAR/3 comparison*):ab,ti) OR ((simulated NEAR/3 treatment* NEAR/3 comparison*):ab,ti) OR ((match* NEAR/4 adjust* NEAR/3 (indirect OR comparison*)):ab,ti) OR ((comparative NEAR/3 effectiveness):ab,ti) OR ((nma NEAR/3 (network OR metaanalysis OR 'meta analysis')):ab,ti) OR ((itc NEAR/3 (indirect OR treatment* OR comparison*)):ab,ti) OR ((mtc NEAR/3 (mixed OR treatment* OR comparison*)):ab,ti) OR ((maicNEAR/4 (match* OR	466782

No.	Query	Results
	adjust* OR indirect OR comparison*)):ab,ti) OR ((stc NEAR/3 (simulated OR treatment* OR comparison*)):ab,ti	
#9	#1 AND #8 AND [2018-2019]/py	10
#10	#7 OR #9	531
#11	rat:ti OR rats:ti OR rodent$:ti OR mouse:ti OR mice:ti OR murine:ti OR hamster$:ti	1703811
#12	#10 NOT #11	528
#13	#12 AND ('chapter'/it OR 'conference review'/it OR 'letter'/it)	7
#14	#12 NOT #13	521
#15	'case report':ti	291457
#16	#14 AND #15	5
#17	#14 NOT #16	516

2.1.4.2 CENTRAL/CDSR search string

The search string for Cochrane Central Register of Controlled Trials (CENTRAL)/ Cochrane Database of Systematic Reviews (CDSR) is presented in Table 6; no study design filters apply to this search.

Table 6: Search string for CENTRAL/CDSR via Cochrane Library

No.	Search	Results
#1	MeSH descriptor: [Mucopolysaccharidosis IV] explode all trees	13
#2	(morquio* OR morqio* OR morkio* OR brailsford* OR keratosulfaturia* OR osteochondrodystrophia* OR GALNS* OR “N acetylgalactosamine 6 sulfatase” OR “N acetylgalactosamine 6 sulfate” OR “n acetyl d galactosamine 6 sulfate 6 sulfohydrolase” OR “n acetyl d galactosamine 6 sulphate 6 sulfohydrolase” OR “n acetylgalactosamine 6 sulphate sulfatase” OR MPSIV* OR “MPS IV” OR “MPS IVA” OR “IV MPS” OR “IVA MPS” OR MPS4* OR “MPS 4” OR “MPS 4A” OR “4 MPS” OR “4A MPS” OR (“typ? 4” OR “typ? iv” OR typ?4 OR typ?iv OR “typ? 4a” OR “typ? iva” OR typ?4a OR typ?iva) NEAR/5 (MPS* OR muco* OR muko*)) OR (typ* NEAR/3 (four OR “4” OR “4A” OR IV OR IVA) NEAR/5 (MPS* OR muco* OR muko*)) OR (familial NEAR/3 osseous NEAR/3 dystrophy) OR (kerato NEAR/3 sulfaturia) OR ((mucopolysaccharidos* OR mucopolysacharidos* OR mukopolysaccharidos* OR “muco polysaccharidosis” OR “muco polysaccharidoses”) NEAR/7 (four OR “4” OR “4A” OR IV OR IVA OR “typeIV” OR “type4”))):ti,ab,kw	116
#3	#1 OR #2 in Cochrane Reviews, Trials	115

2.1.4.3 PubMed search string

PubMed was searched to capture in-process or e-publications ahead of print, with the search string presented in Table 7. RCTs were identified using the Cochrane handbook’s Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format, was used, without the final two rows (see lines #2 to #8 below).

Table 7: Search string for in-process and e-publications ahead-of-print via PubMed

No.	Query	Results
#1	Search ("Mucopolysaccharidosis IV"[mh] OR morquio*[tiab] OR morqio*[tiab] OR morkio*[tiab] OR brailsford*[tiab] OR keratosulfaturia*[tiab] OR osteochondrodystrophia*[tiab] OR GALNS*[tiab] OR “N acetylgalactosamine 6 sulfatase”[tiab] OR “N acetylgalactosamine 6 sulfate”[tiab] OR “n acetyl d galactosamine 6 sulfate 6 sulfohydrolase”[tiab] OR “n acetyl d galactosamine 6 sulphate 6 sulfohydrolase”[tiab] OR “n acetylgalactosamine 6 sulphate sulfatase”[tiab] OR MPSIV*[tiab] OR “MPS IV”[tiab] OR “MPS IVA”[tiab] OR “IV MPS”[tiab] OR “IVA MPS”[tiab] OR MPS4*[tiab] OR “MPS 4”[tiab] OR “MPS 4A”[tiab] OR “4 MPS”[tiab] OR “4A MPS”[tiab] OR ((“typ? 4”[tiab] OR “typ? iv”[tiab] OR typ?4[tiab] OR typ?iv[tiab] OR “typ? 4a”[tiab] OR “typ? iva”[tiab] OR typ?4a[tiab] OR typ?iva[tiab]) AND (MPS*[tiab] OR mucopoly*[tiab] OR muko*[tiab])) OR (type*[tiab] AND (four[tiab] OR “4”[tiab] OR “4A”[tiab] OR IV[tiab] OR IVA[tiab]) AND (MPS*[tiab] OR mucopoly*[tiab] OR muko*[tiab])) OR (familial[tiab] AND osseous[tiab] AND dystrophy[tiab]) OR (kerato[tiab] NEAR/3 sulfaturia[tiab]) OR ((mucopolysaccharidos*[tiab] OR mucopolysacharidos*[tiab] OR mukopolysaccharidos*[tiab] OR “muco polysaccharidosis”[tiab] OR “muco polysaccharidoses”[tiab]) AND (four[tiab] OR “4”[tiab] OR “4A”[tiab] OR IV[tiab] OR IVA[tiab] OR “typeIV”[tiab] OR “type4”[tiab]))))	3194
#2	Search "Clinical Trials as Topic"[Mesh:NoExp]	188696
#3	Search (“randomized controlled trial”[pt] OR “controlled clinical trial”[pt])	580502
#4	Search (randomized[tiab] OR randomised[tiab] OR placebo*[tiab] OR randomly[tiab] trial[ti])	145727
#5	Search (“Cohort Studies”[mh] OR “Longitudinal Studies”[mh] OR “Prospective Studies”[mh] OR “Follow-Up Studies”[mh] OR “Case-Control Studies”[mh] OR cohort*[tw] OR ((case[tw] OR cases[tw]) AND (control*[tw] OR series[tw]))))	2877757
#6	Search (“non randomized”[tw] OR “non randomised”[tw] OR nonrandomized[tw] OR nonrandomised[tw] OR ((controlled[tw] OR extension[tw]) AND (trial*[tw] OR study[tw] OR studies[tw] OR phase[tw]))))	1142793
#7	Search (“registries”[mh] OR register[tiab] OR registry[tiab])	195300
#8	Search (#2 OR #3 OR #4 OR #5 OR #6 OR #7)	3923199
#9	Search (#1 AND #8)	527
#10	Search (“Meta-Analysis”[pt] OR "Network Meta-Analysis"[mh] OR metaanalysis[tiab] OR “meta analysis”[tiab] OR “meta regression”[tiab] OR “adjusted indirect comparison”[tiab] OR (systematic*[tiab] AND review*[tiab]) OR ((mixed[tiab] OR indirect[tiab]) AND treatment*[tiab] AND comparison*[tiab]) OR (simulated[tiab] AND treatment*[tiab] AND comparison*[tiab]) OR (match*[tiab] AND adjust*[tiab] AND (indirect[tiab] OR comparison*[tiab])) OR (comparative[tiab] AND effectiveness[tiab]) OR (nma[tiab] AND (network[tiab] OR metaanalysis[tiab] OR “meta analysis”[tiab])) OR (itc[tiab] AND (indirect[tiab] OR treatment*[tiab] OR comparison*[tiab])) OR (mtc[tiab] AND (mixed[tiab] OR treatment*[tiab] OR comparison*[tiab])) OR (maic[tiab] AND (match*[tiab] OR adjust*[tiab] OR indirect[tiab] OR comparison*[tiab])) OR (stc[tiab] AND (simulated[tiab] OR treatment*[tiab] OR comparison*[tiab]))))	319885
#11	Search ((#1 AND #10)) AND ("2018/01/01"[Date - Publication] : "3000"[Date - Publication])	12
#12	Search (#9 OR #11)	533
#13	Search (rat[ti] OR rats[ti] OR rodent[ti] OR mouse[ti] OR mice[ti] OR murine[ti] OR hamster[ti] OR hamsters[ti])	1415407
#14	Search (#12 NOT #13)	527
#15	Search (pubstatusaheadofprint OR inprocess[sb])	776692

No.	Query	Results
#16	Search (#14 AND #15)	19

2.2 Clinical SLR update – June 2021

The majority of the methodology for the 2021 update of the clinical SLR was aligned with that utilised in the 2019 SLR, with the exception that the electronic databases were searched via Ovid rather than Embase.com, and that searches were date limited to identify only those studies published post-October 2019. Identified citations were first screened based on title/abstract and subsequently by full text by a single researcher. All citations were screened by a second independent researcher at both the title/abstract and full text screening stages, with disputes as to eligibility referred to a strategic advisor and resolved by consensus.

2.2.1 Updated eligibility criteria

The eligibility criteria for the clinical SLR were also amended to allow for the identification of studies published post-2019, relating to standard of care for MPS IVa other than ERT (reported as full publications and enrolling >5 subjects) (Table 8).

Table 8. Eligibility criteria for clinical studies

Characteristic	Inclusion criteria
Population	• MPS IVa (Morquio syndrome) • Any age group (children or adults)
Mixed populations	• Data reported for paediatric and adult populations (mixed data) is also eligible. Where reported separately, the mixed and separate population data will be extracted
Interventions/ comparators	• In MPS IVa: o At least one treatment arm has a dose of ERT o No treatment o Standard of care for symptom management
Outcomes	• Study reports any of the following outcomes of interest: o Endurance assessments (6MWT, T25FW/MSFC, stair climb test, pinch/grip test, functional dexterity test, cardiac and antibody titres) o Pain o Fatigue o Psychological assessments o Urinary KS o Heart function o Lung function o Survival o Audiometry tests o Sleep apnoea o Corneal clouding o Muscle strength o HRQoL, MPS HAQ and ADL (listed only)
Study design	• RCTs, non-RCTs, single arm/case series • SLRs/NMAs*
Date limits	• Studies published post October 2019
Child abstract	• Sub-study abstract with unique data that could be refered to
Publication type	• Errata • Original articles • Technology appraisal documents, if original source not available elsewhere
Languages	• Electronic searching not limited to English

*Relevant SLRs and meta-analyses were kept in at first pass for cross-referencing/bibliography checking purposes but were excluded at second pass.

Abbreviations: ADL, activities of daily living; ERT, enzyme replacement therapy; ESA, Elosulfase alfa; HRQoL, Health Related Quality of Life; HSCT, hematopoietic stem cell transplantation; MPS HAQ, mucopolysaccharidosis health assessment questionnaire; MPS IVa, Mucopolysaccharidosis type IVa; MSFC, multiple sclerosis functional composite; 6MWT, 6-minute walk test; NMA, Network meta-analysis; SLR, systematic literature review; T25FW, timed 25-foot walk test.

2.2.2 Updated search strategy

Due to the anticipated low number of citations for screening based on title and abstract, the updated search strategies were restricted to the disease-related search terms from the 2019 clinical SLR. No search

filters for study design or publication type were included in the search strings. Conference searches were also conducted for the WORLD and SSIEM conferences held since October 2019 using the same search terms as the 2019 clinical SLR. The updated searches were conducted on 30th June 2021.

Table 9: Search string for Embase via Ovid*

#	Searches	Results
1	exp Morquio syndrome/	1339
2	(morquio$ or morqio$ or morkio$ or Brailsford$ or keratosulfaturia$ or osteochondrodystrophia$ or galns$ or 'n acetylglactosamine 6 sulfatase' or 'n acetylgalactosamine 6 sulfate' or 'n acetyl d galactosamine 6 sulfate 6 sulfohydrolase' or 'n acetyl d galactosamine 6 sulphate 6 sulfohydrolase' or 'n acetylgalactosamine 6 sulphate sulfatase' or mpsiv$ or 'mps iv' or 'mps iva' or 'iv mps' or 'iva mps' or mps4* or 'mps 4' or 'mps 4a' or '4 mps' or '4a mps').ti,ab,hw.	2045
3	(('typ? 4' or 'typ? iv' or typ?4 or typ?iv or 'typ? 4a' or 'typ? iva' or typ?4a or typ?iva) adj5 (mps$ or muco$ or muko$)).ti,ab,hw.	675
4	(typ$ adj3 (four or '4' or '4a' or iv or iva) adj5 (mps$ or muco$ or muko$)).ti,ab,hw.	921
5	(familial adj3 osseous adj3 dystrophy).ti,ab,hw.	1
6	(kerato adj3 sulfaturia).ti,ab,hw.	0
7	((mucopolysaccharidos$ or mucopolysacharidos$ or mukopolysaccharidos$ or 'muco polysaccharidosis' or 'muco polysaccharidoses') adj7 (four or '4' or '4a' or iv or iva or 'typeiv' or 'type4')).ti,ab,hw.	738
8	or/1-7	2790
9	limit 8 to yr="2019 -Current"	367

*1974 to 2021 June 29

Table 10: Search string for MEDLINE via Ovid*

#	Searches	Results
1	Mucopolysaccharidosis IV/	1179
2	(morquio$ or morqio$ or morkio$ or Brailsford$ or keratosulfaturia$ or osteochondrodystrophia$ or galns$ or 'n acetylglactosamine 6 sulfatase' or 'n acetylgalactosamine 6 sulfate' or 'n acetyl d galactosamine 6 sulfate 6 sulfohydrolase' or 'n acetyl d galactosamine 6 sulphate 6 sulfohydrolase' or 'n acetylgalactosamine 6 sulphate sulfatase' or mpsiv$ or 'mps iv' or 'mps iva' or 'iv mps' or 'iva mps' or mps4* or 'mps 4' or 'mps 4a' or '4 mps' or '4a mps').ti,ab,hw.	1150
3	(('typ? 4' or 'typ? iv' or typ?4 or typ?iv or 'typ? 4a' or 'typ? iva' or typ?4a or typ?iva) adj5 (mps$ or muco$ or muko$)).ti,ab,hw.	389
4	(typ$ adj3 (four or '4' or '4a' or iv or iva) adj5 (mps$ or muco$ or muko$)).ti,ab,hw.	532
5	(familial adj3 osseous adj3 dystrophy).ti,ab,hw.	1
6	(kerato adj3 sulfaturia).ti,ab,hw.	0
7	((mucopolysaccharidos$ or mucopolysacharidos$ or mukopolysaccharidos$ or 'muco polysaccharidosis' or 'muco polysaccharidoses') adj7 (four or '4' or '4a' or iv or iva or 'typeiv' or 'type4')).ti,ab,hw.	1414
8	or/1-7	2146
9	limit 8 to yr="2019 -Current"	190

*MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R): 1946 to June 29, 2021

Table 11: Search string for EBM Reviews via Ovid*

#	Searches	Results
1	Mucopolysaccharidosis IV/	15
2	(morquio$ or morqio$ or morkio$ or brailsford* or keratosulfaturia$ or osteochondrodystrophia$ or galns$ or 'n acetylglactosamine 6 sulfatase' or 'n acetylgalactosamine 6 sulfate' or 'n acetyl d galactosamine 6 sulfate 6 sulfohydrolase' or 'n acetyl d galactosamine 6 sulphate 6 sulfohydrolase' or 'n acetylgalactosamine 6 sulphate sulfatase' or mpsiv$ or 'mps iv' or 'mps iva' or 'iv mps' or 'iva mps' or mps4* or 'mps 4' or 'mps 4a' or '4 mps' or '4a mps').ti,ab,kw.	66
3	(('typ? 4' or 'typ? iv' or typ?4 or typ?iv or 'typ? 4a' or 'typ? iva' or typ?4a or typ?iva) adj5 (mps$ or muco$ or muko$)).ti,ab,kw.	10
4	(typ$ adj3 (four or '4' or '4a' or iv or iva) adj5 (mps$ or muco$ or muko$)).ti,ab,kw.	22
5	(familial adj3 osseous adj3 dystrophy).ti,ab,kw.	0
6	(kerato adj3 sulfaturia).ti,ab,kw.	0
7	((mucopolysaccharidos$ or mucopolysacharidos$ or mukopolysaccharidos$ or 'muco polysaccharidosis' or 'muco polysaccharidoses') adj7 (four or '4' or '4a' or iv or iva or 'typeiv' or 'type4')).ti,ab,kw.	44
8	or/1-7	86
9	limit 8 to yr="2019 -Current"	4

*Cochrane Central Register of Controlled Trials May 2021, Cochrane Database of Systematic Reviews 2005 to June 23, 2021

2.2.3 Summary of non-ERT studies identified

A total of 11 studies were identified which reported on the incidence and/or longitudinal outcome in patients with MPS IVa. The following symptoms/abnormalities were reviewed across the studies:

- Respiratory (n=2) (1, 2)
- Cardiac (n=2) (3, 4)
- Correction of spinal lesions (n=1) (5)
- Orthopaedic (n=1) (6)
- Ophthalmology (n=1) (7)
- Sleep disruption (n=1) (8)
- Anthropomorphic features (n=1) (9)
- Otorhinolaryngology (n=1) (10)
- Functional outcomes (n=) (11)

Details of study design, enrolled patients, and principal findings are summarised in Table 12. None of the studies identified were considered relevant for informing data/model inputs related to standard of care in this submission.

Table 12: Summary of non-ERT studies reported as full publications and enrolling >5 subjects with MPS IVa

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
Averil 2021 (1) Medical record review USA	To characterise tracheal abnormalities in children and adults with MPS IVa including interplay of the trachea, vasculature, bones and thyroid at the thoracic inlet.	N with MPS IVa, N=37 Mixed adult/paediatric subjects Median age, 18.1 years (SD 9.5; range 1.1–43.7) Gender: • Paediatric, 9/20 female	ERT treatment details: unclear	Main findings: • Mean (range) tracheal cross-sectional area narrowing at the thoracic inlet, 63.9% (−2.1 to 96%) • Trend for increased tracheal narrowing in older children • Trachea commonly deviated rightward	Narrowing, deviation and abnormal shape of the trachea at the thoracic inlet are common in children and adults with MPS IVa, with a trend toward increased narrowing with advancing age in children. A W- or T-shaped trachea is associated with focal tracheal narrowing.

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
		• Adult, 10/17 female		posterior (22/37 subjects, 59%) • T- or W-shaped tracheas had two times greater tracheal narrowing than D- or U-shaped tracheas ($p<0.05$) • Brachiocephalic artery was tortuous in 35/37 subjects with direct impingement on the trachea in 24/37 subjects. • Thyroid located in the thoracic inlet in 28/37 subjects; significantly associated with tracheal narrowing ($p=0.016$)	Crowding of the thoracic inlet, due to vascular tortuosity and thyroid position, appears to play a major role.
Ayuna 2021 (3) Retrospective cohort study UK/South Africa	To review current practice and suggest best practice guidelines regarding the frequency of cardiac rhythm monitoring in patients with MPS	N with MPS IVa, N=19 Adult subjects (diagnosed in paediatric) Median age (range) across total MPS cohort (n=77): • Male, 27 years (18-55) • Female, 27.5 (18‑65)	ERT treatment details: 42 of total MPS cohort (n=77) received ERT (n=19, no treatment)	12-lead ECG data available for 7 MPS VI subjects: • Sinus rhythm, n=7 • LVH, n=1 • Early repolarisation, n=3 • Partial RBBB, n=1 • Right axis deviation, n=1 • Bifascicular block, n=1	Regular cardiac monitoring is required to warrant early detection of underlying conduction tissue abnormalities. In addition [12-lead ECG is the first line investigation that, if abnormal, should be followed up by 24-hour Holter monitoring].

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
		Gender across total cohort • Male, n=49/77		• T wave inversion in lead III only, n=2 24-hour ECG data available for 4 MPS VI subjects: • Sinus tachycardia, n=1 • Extra systolic beats, n=3 o premature ventricular contraction, n=2; supraventricular ectopic (VE) beat, n=1). [None of subjects had AF, atrial flutter or any other form of tachyarrhythmia or bradyarrhythmia]	
Kenth 2019 (2) Retrospective cohort study UK [Publication reports additional data to that reported in the separate	To report the longitudinal characterisation of pulmonary function changes in children with MPS IVa	N with MPS IVa, N=16[§] Paediatric subjects Median age at diagnosis, 34 months (range: 14-161; IQR 62.75) Male gender, n=7/16	ERT treatment details: 13/16 subjects received ERT Median age of commencing ERT, 78 months (IQR 77.5; 10th percentile 38.4, 90th percentile 179.8)	Main findings (reported in Kenth 2019b): • In general, during the study period there was a global reduction in static spirometry values in all subjects, as well as the 6MWT, with the decline being delayed in the ERT group (versus non-ERT)	Whilst spirometry values showed a gradual decline across all groups, oximetry showed modest improvement in respiratory function

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
research article by Kenth 2019b)(12)				• Oximetry changed to a minor degree over time in the ERT group, whereas it declined in the non-ERT group. • NIV and adenotonsillectomy were more effective in the ERT group (versus non-ERT group), either improving pulmonary function or attenuating deterioration	
Lee 2019 (11) Retrospective cohort study Taiwan	To administer the Functional Independence Measure for Children (WeeFIM) questionnaire to ascertain functional strengths and weaknesses of patients with MPS	N with MPS IVa, N=12 Mixed adult/paediatric subjects Median age across total MPS cohort (n=63), 13 years, 3 months Gender across total cohort • Male, n=37/63	ERT treatment details: 7/12 patients received ERT	Mean self-care score† (median) [range] • 36 (35) [11-56] Mean mobility score† (median) [range] • 24 (25) [10-35] Mean cognition score† (median) [range] • 32 (35) [19-35] Mean total score† (median) [range] • 92 (97) [48-126]	Patients with MPS require support and supervision in self-care tasks.

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
				Patients with MPS IVa treated with ERT (n=7) had higher scores (less dependence) in self-care and mobility domains than patients without ERT (n=5)	
Lin 2020 (4) Retrospective cohort study Taiwan	To characterise cardiac abnormalities in subjects with MPS	N with MPS IVa, N=14 Mixed adult/paediatric subjects Median age [SD] (range), 13.3 years [7.6] (2.3-28.0) Male gender, n=6/14	ERT treatment details: 7/14 subjects received ERT	Mean z scores (SD) • GLS, 0.58 (1.65) • LVMI, -0.07 (1.69) • IVSd, 1.29 (1.06) • LVPWd, 0.79 (0.78) • AoD, 4.30 (2.02) Mean severity score of valvular heart disease • Mitral stenosis, 0.00 • Mitral regurgitation, 0.86 • Aortic stenosis, 0.00 • Aortic regurgitation, 0.39 Left ventricular remodelling patterns, N (%) • Normal, 10 (71) • Concentric remodelling, 3 (21)	The most significant left ventricular myocardial deformation, hypertrophy and valvular heart disease were observed in the patients with MPS VI, II, and I, followed by those with MPS IV. Cardiac abnormalities in patients with MPS worsened with increasing age in accordance with the progressive nature of the disease.

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
				• Eccentric hypertrophy, 1 (7) • Concentric hypertrophy, 0 (0)	
Miao 2020 (6) Medical record review China	To examine the hip morphology of paediatric patients with MPS type IVa	N with MPS IVa, N=21 (42 hips) Paediatric subjects Mean age (SD) at the time of radiography, 66.3 months (21.7)	ERT treatment details: unclear	MRI-assessed acetabular index, mean (SD) • Bony, 36.3° (5.3) • Cartilaginous, 18.3° (4.7) • Labral, 12.1° (4.6) MRI assessment of labrum, n/N • Regular triangle, 12/42 • Flat, 30/42 Mean (SD) arthrographic acetabular index, 11.1° (2.7)	Hips in MPS IVa exhibit obvious cartilage and labrum compensation in response to abnormal ossification of bony acetabulum. Cartilage in MPS IVa hip increases the thickness in the longitudinal direction, while the labrum becomes flatten in the horizontal direction.
Murgasova 2020 (10) Retrospective cohort study Czech Republic	To characterise ENT diagnoses in subjects with MPS	N with MPS IVa, N=17 Paediatric subjects Median age at time of manifestation of the first ENT symptoms across total MPS cohort (n=61), 2.8 years (range 0.1–19.3)	ERT treatment details: unclear	Frequency of ENT symptoms, % • Otitis media with effusion, 43% • Mild-to-moderate hearing loss, 67% • Upper airway obstruction, 27% • Acute otitis media, 47%	A high and early occurrence of various otolaryngologic symptoms in MPS was reported, highlighting the role of ENT specialists in prompt diagnosis and long-term management.

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
		Median age at time of diagnosis of MPS across total cohort, 4.1 years Gender across total cohort • Male, n=36/61		• Chronic/recurrent rhinosinusitis, 50% Requirement for ENT surgeries, % • Adenoidectomy, 47% • Tympanostomy, 27%	
Remondino 2020 (5) Retrospective cohort study Argentina	To describe clinical manifestations and surgical management and outcomes of spinal lesions in subjects with MPS	N with MPS IVa, N=22 Paediatric subjects Mean age [SD] (range) at diagnosis across total MPS cohort (n=52), 8 years [4] (1-19) Mean (SD) age at surgery, 7 (2) years Gender across total cohort • Male, n=32/52 Mean (SD) follow up, 11 (8) years	ERT treatment details: unclear	Across the total MPS cohort (n=52): • Cervical disease, n=43/52 (most frequent indication odontoid hypoplasia followed by atlantoaxial instability) • Thoracolumbar kyphosis, n=14/52 • Presentation with neurologic compromise prior to surgery, n=21 (quadriparesis the most frequent manifestation) • Progression of neurologic impairment the most common surgical indication • Surgery performed in 38/52 patients:	Early spinal cord decompression is recommended in MPS spine pathology to prevent or potentially reverse neurologic impairment.

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
				o Cervical, n=25 o Thoracolumbar, n=13 • 6/21 patients with preoperative neurologic deficit showed neurologic improvement post-surgery	
Rozdzynska-Swiatkowska 2020 (9) Retrospective cohort study Poland	To create a pattern of face and body stature based on anthropometric measurements taken from a cohort of patients with MPS IVa	N with MPS IVa, N=20 Paediatric subjects Mean age (SD) [range], 9 years [10.7] (3 months to 26 years) Male gender, n=13/20	ERT treatment details: untreated	Body weight, mean (SD) • MPS IVa cohort, 3,719.3 g (461) • Healthy general population, 3,500 g (600), p=0.35 Body length, mean (SD) • MPS IVa cohort, 57.3 cm (3.34) • Healthy general population, 52.2 cm (2.8), p=0.003 Other reported features in patients with MPS IVa included: • Skeletal abnormalities: narrow shoulders and narrow and convex chest	Multiple anthropometric measurements, including age ranges, allowed for the creation of a model that indicated the most characteristic features of the MPS IVa phenotype

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
				• Relatively elongated head and neck in comparison to body height, and tucked between narrow shoulders • Head reported to have dolichocephalic shape, while the nose was short with wide nostrils	
Tural 2021 (8) Retrospective, cross-sectional study Turkey	To evaluate the prevalence of SDB by using PSG in children with MPS IVa and MPS VI who underwent ERT and to analyse the effect on SDB of undergoing upper airway surgery, pulmonary functions, and exercise capacity	N with MPS IVa, N=17 Paediatric subjects Mean age [SD] (range) at initiation of ERT across total MPS cohort (n=28), 5.1 years [3.7] (6 months to 14 years) Mean age [SD] at time of diagnosis across total MPS cohort, 3.0 years [2.8] Gender across total cohort • Male, n=13/28	ERT treatment details: all subjects received ERT (median treatment duration across total MPS cohort, 3.7 years)	Severity of sleep apnea (AHI) • None, n=4/17 • Mild, n=4/17 • Moderate, n=9/17 • Severe, n=2/17 Polysomnographic findings, median (range) • Total sleep time (min), 347.1 (146.5–398.4) • Sleep latency (min), 37.0 (1.0–87.5) • REM latency (min), 157.0 (90.0–300.5) • AHI total (events/hr), 1.7 (0.2–50.8)	Despite ERT and previous upper airway surgery, the prevalence of OSA was high in patients with MPS IVa-MPS IV, emphasising the importance of PSG screening for sleep disorders. Pulmonary function tests may be useful for predicting sleep apnea in patients with MPS IVa and MPS VI.

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
				Pulmonary function tests, median (range) (N=13) • FEV1%, 107.1 (75.0–155.0) • FVC%, 97.0 (72.0–127.0) • FEV1/FVC%, 90.1 (80.4–115.0) • FEF 25-75%, 107.0 (30.3–146.0) 6MWT, median (range) • Walking distance (m), 349.0 (241.0–443.0) • %, 87.4 (63.0–150.5)	
Zhang 2020 (7) Prospective, cross-sectional study Taiwan	To evaluate the anterior chamber angle status and estimate IOP in patients with MPS type I, II, IV, and VI	N with MPS IVa, N=9 Male gender, n=2/9	ERT treatment details: unclear	Principal findings: • All patients had mild-to-moderate clouded corneas bilaterally (total 18 eyes) • CCT right eye (mm), 513.00 (49.36) • CCT left eye (mm), 529.11 (62.32) mm • Bilateral elevated CVS-IOP corrected estimates, n=4/9 (8 eyes)	MPS type IV patients are vulnerable to open-angle glaucoma

Author, study design, country	Aim	Patient population	Treatment	Principal findings in MPS IVa patients	Author conclusion
				• OCT revealed normal open-angle structures in all eyes	

Abbreviations: 6-MWT: 6-minute walking test; AHI, apnea-hypopnea index; AoD, aortic diameter; CCT, central corneal thickness; ECG, electrocardiogram; ENT, ear, nose, and throat; ERT, enzyme replacement therapy; FEF 25–75, forced expiratory flow from 25% to 75% of vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GLS, global longitudinal strain; IOP, intraocular pressure; IQR, inter-quartile range; IVSd, interventricular septum thickness in diastole; LTBD, laryngotracheobronchial disease; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness in diastole; MPS, mucopolysaccharidosis; MRI, magnetic resonance imaging; NIV, non-invasive ventilation; OCT, optical coherence tomography; OSA, obstructive sleep apnea; PSG, polysomnography; RBBB, right bundle branch block; REM, rapid eye movement; SD, standard deviation; SDB, sleep-disordered breathing; WeeFIM, Functional Independence Measure for Children

†Maximum possible scores: total 126; self-care 56; motility 35; cognition 35.

‡Normal sleep was defined as total AHI <1.0/h, mild sleep apnea as AHI ≥1.0/h–<5.0/h, moderate sleep apnea as AHI ≥5.0/h–<10.0/h, and severe sleep apnea as AHI ≥10.0/h.

§Subjects in this study included those from the MOR 100 phase 1 study (n=5), MOR 005 phase III placebo-controlled (n=5) and the MOR 007 trial (n=6)

¶This publication reports supplemental data to that reported in the related publication, Kenth JJ et al. The Characterization of Pulmonary Function in Patients with Mucopolysaccharidoses IVa: A Longitudinal Analysis. Mol Genet Metab Rep. 2019 Jul 12;20:100487. This publication was identified in the original clinical SLR conducted in October 2019.

2.3 Clinical efficacy data

2.3.1 Statistical methods

2.3.1.1 Collation of a unified Managed Access Agreement (MAA)/MOR-001 dataset

A flat file (i.e., a single file containing all data across all patients and relevant outcomes) was required to perform statistical analyses. The ERG highlighted issues with the previous submitted flat file including uncertainty about any post-hoc changes to the data and concerns around the method used to define timepoints in MOR-001 patients; after consultation with NICE and the ERG during technical engagement, it was decided that a new flat file would be generated using the original BioMarin Microsoft Access database. Any data cleaning and interpretation of results was recorded to ensure a paper trail for the analyses conducted.

2.3.1.1.1 Data sources used to generate the new flat file

Several data sources were utilized to generate the new flat file. These data sources are listed below in Table 13. In addition to the data sources listed above, additional information was provided by clinicians involved in the MAA who were consulted in the interviews described in Section 2.5. The data added as a result of these interviews are presented in Section 2.3.1.1.5 (Table 18).

Table 13: Data sources used to generate the new flat file

Data	Data source	Data on file†
MAA patient-level data	BioMarin Access database (November 2019)	MAA Database- 01112019 - LC.accdb
MAA trial levels (Trial, Trial_Level2, Trial_Level3)	Injected from previous BioMarin flat file	Main_dataset_v07.xlsx
MOR-001 patient-level data at baseline, 6MWT beyond baseline	Injected from previous BioMarin flat file; timepoints altered using methods described in "Adjustment of timepoints from the MOR-001 study"	Main_dataset_v07.xlsx
MOR-001 patient-level data for MPS-HAQ data beyond baseline	Injected from MOR-001 raw data file for MPS-HAQ; timepoints altered using methods described in "Adjustment of timepoints from the MOR-001 study"	ha2_mor001_26JAN21.csv
MOR-001 patient-level data for FEV_1 and FVC beyond baseline	Injected from MOR-001 raw data file for respiratory outcomes; timepoints altered using methods described in "Adjustment of timepoints from the MOR-001 study"	rsp_mor001_26JAN21.csv

Abbreviations: 6MWT, 6-minute walk test; FEV_1, forced expiratory volume; FVC, forced vital capacity; MAA, managed access agreement; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire. †Data on file documents are available from BioMarin upon request.

2.3.1.1.2 Adjustment of timepoints from the MOR-001 study

The ERG highlighted issues with the MOR-001 data which was provided in the resubmission. The main concern surrounded the labelling of time points for MOR-001 patients and whether values labelled as, for example, Year 1 and Year 2, were truly captured at Year 1 and Year 2.

To address this, the date of assessment was used to determine the appropriate time point. Study entry was assumed to be the date of baseline. For all data points the study entry date was subtracted from the date of assessment to determine the number of days in the study the data were captured at; these were converted into months (assuming 365.25 days in a year).

The MOR-001 time points were then compared against the Managed Access Agreement (MAA) time points on a per-outcome basis; for example, a list of unique time points captured for 6MWT in the MAA patient population was generated as shown in Table 14.

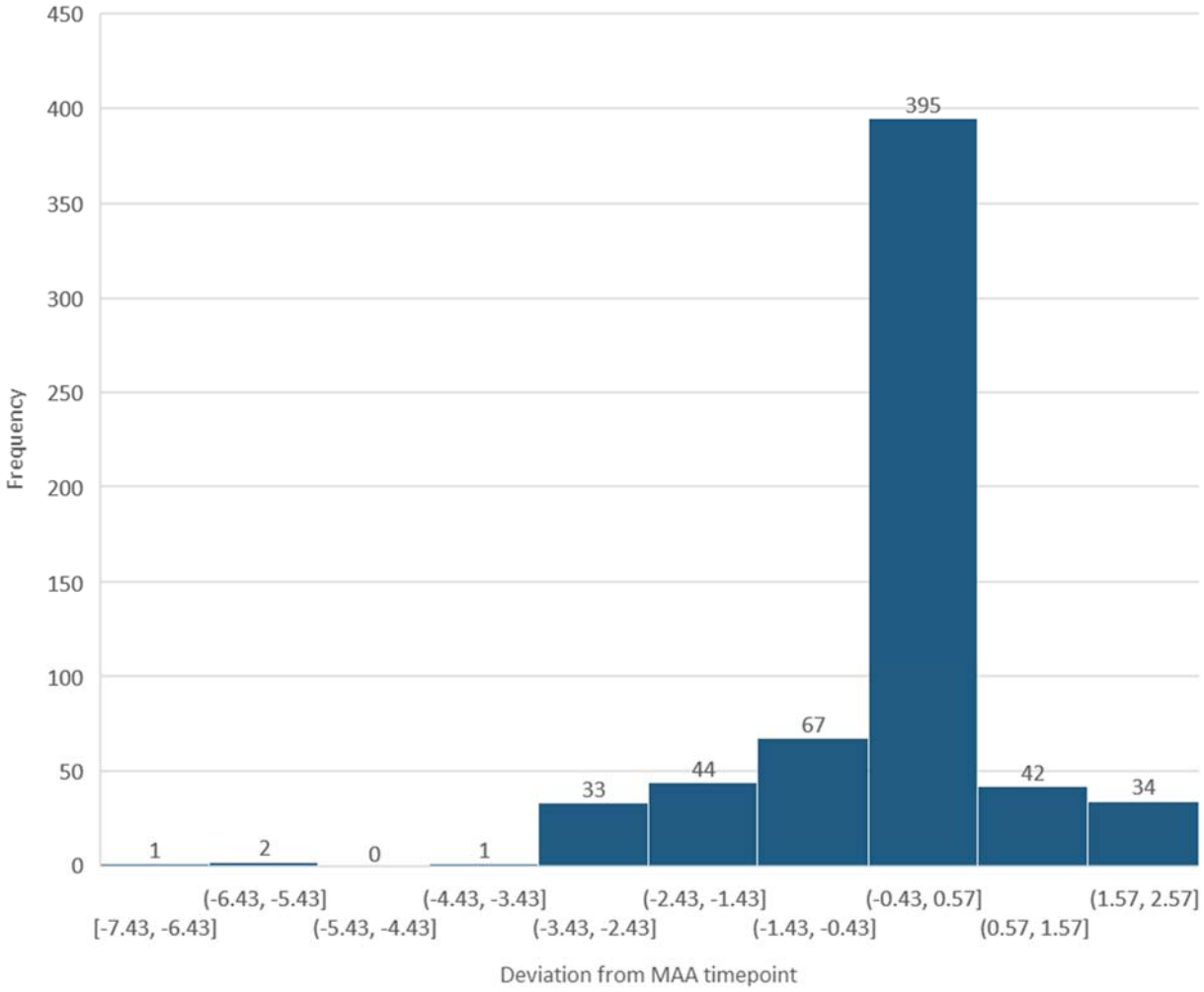
Table 14: List of unique time points in MAA dataset for 6MWT

MAA unique time points for 6MWT	Time from baseline (months)
Baseline	0
4 months	4
12 months	12
18 months	18
20 months	20
24 months	24
36 months	36
42 months	42
48 months	48

Abbreviations: 6MWT, 6-minute walk test; MAA, managed access agreement.

The “months from baseline” values generated for MOR-001 were matched against the closest pre-existing time point from the MAA. As expected, some deviance of the “true” timepoint versus the nearest MAA timepoint existed, as shown in Figure 1. The rounded absolute deviations from each of the nearest MAA timepoints are shown in Table 15. 94.51% of MOR-001 time from baseline values for 6MWT were rounded to an MAA timepoint within 2 months of the “true” MOR-001 time from baseline. Three extreme values were identified with deviations of -7.42, -5.98 and -5.78 months; these values appear to have been values captured at around year 5 of MOR-001. These values do not feature in any analyses as complete case analyses were only performed up to 3 years due to a scarcity of complete cases beyond 3 years.

Figure 1: Histogram of deviation of true MOR-001 timepoint versus nearest matched MAA timepoint for 6MWT



Abbreviations: 6MWT, 6-minute walk test; MAA, managed access agreement.

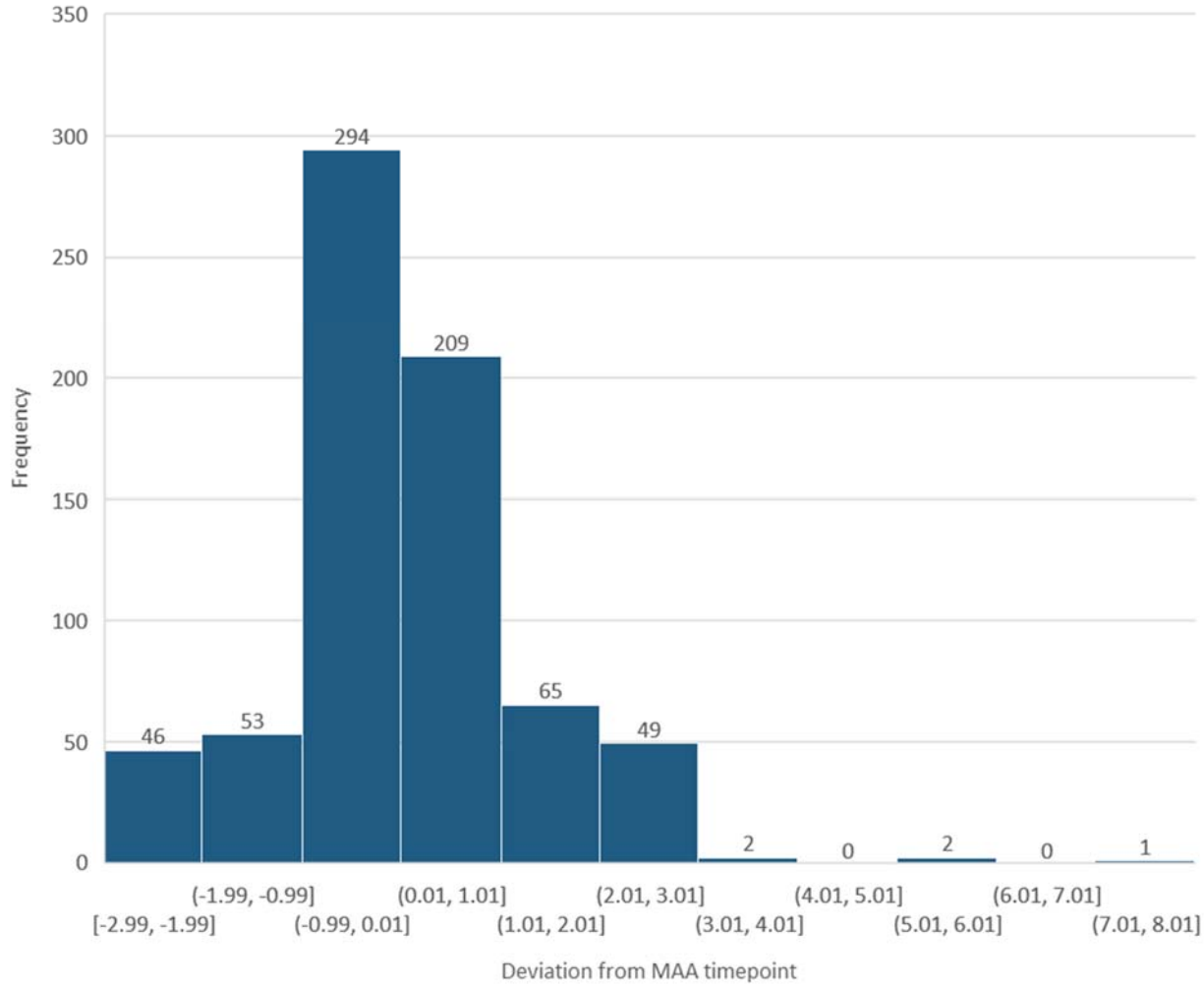
Table 15: Distribution of discrepancies from MAA timepoints for 6MWT results

Rounded absolute deviation from MAA timepoint (0 d.p.)	Number of datapoints	Proportion of datapoints
0	392	63.33%
1	117	18.90%
2	76	12.28%
3	31	5.01%
6†	2	0.32%
7†	1	0.16%
Total	619	100%

Abbreviations: 6MWT, 6-minute walk test; d.p., decimal places; MAA, managed access agreement. †Values do not feature in any analyses due to a lack of complete cases.

The timepoint matching process described above was also performed for Mucopolysaccharidosis Health Assessment Questionnaire (MPS-HAQ) Q33 and Q33a, forced expiratory volume in 1 second (FEV_1), and forced vital capacity (FVC) values. Deviance from the MAA timepoints for MPS-HAQ assessment dates are shown in Figure 2 and Table 16; 92.65% of values were mapped to a timepoint within 2 months of the "true" MOR-001 time from baseline. As for the 6MWT data, there were three extreme outliers (discrepancies of 5–7 months around 4 and 5 years) which were not considered in the analysis due to a lack of complete cases.

Figure 2: Histogram of deviation of true MOR-001 timepoint versus nearest matched MAA timepoint for MPS-HAQ questions 33 and 33a



Abbreviations: MAA, managed access agreement; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire.

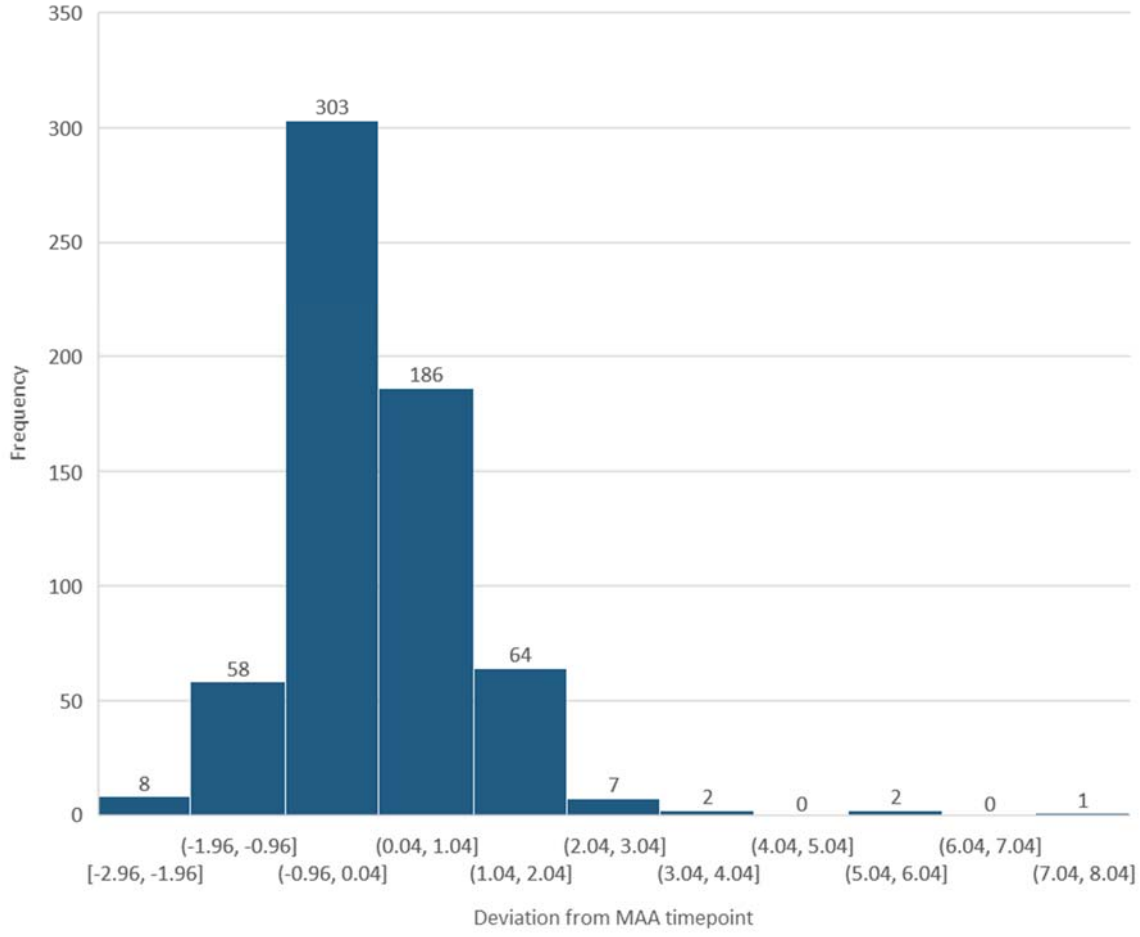
Table 16: Distribution of discrepancies from MAA timepoints for MPS-HAQ questions 33 and 33a results

Rounded absolute deviation from MAA timepoint (0 d.p.)	Number of datapoints	Proportion of datapoints
0	429	59.50%
1	138	19.14%
2	101	14.01%
3	49	6.80%
4	1	0.14%
6†	2	0.28%
7†	1	0.14%
Total	721	100%

Abbreviations: d.p., decimal places; MAA, managed access agreement; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire. †Values do not feature in any analyses due to a lack of complete cases.

Timepoint discrepancies for FEV_1 and FVC are shown in Figure 3 and Table 17. FEV_1 and FVC were captured at the same assessment times and so are not presented separately (the discrepancies and histograms would be identical).

Figure 3: Histogram of deviation of true MOR-001 timepoint versus nearest matched MAA timepoint for FEV_1 and FVC



Abbreviations: FEV_1, forced expiratory volume; FVC, forced vital capacity; MAA, managed access agreement.

For the analysis, 99.68% of values were mapped to a timepoint within 2 months of the "true" MOR-001 time from baseline. As for the 6MWT and MPS-HAQ data, there were three extreme outliers (discrepancies of 5–7 months around 4 and 5 years) which were not considered in the analysis due to a lack of complete cases.

Table 17: Distribution of discrepancies from MAA timepoints for FEV_1 and FVC results

Rounded absolute deviation from MAA timepoint (0 d.p.)	Number of datapoints	Proportion of datapoints
0	397	63.93%
1	157	25.28%
2	65	10.47%
3	8	1.29%
4	1	0.16%
6†	2	0.32%
7†	1	0.16%
Total	631	100%

Abbreviations: d.p., decimal places; FEV_1, forced expiratory volume; FVC, forced vital capacity; MAA, managed access agreement.
†Values do not feature in any analyses due to a lack of complete cases.

2.3.1.1.3 Generation of an MAA database flat file

The original Microsoft Access database (dated November 2019) containing the raw MAA data was accessed and used as a starting point. Tables of key outcome data were extracted from the MAA database and imported into Excel worksheets. The data were then transformed into a single flat file which contained all data across all relevant outcomes and time points.

The trial status of the patient and their treatment status were obtained from the previous submitted flat file as these were nonclinical data and would not have been subjected to any potential post-hoc cleaning.

2.3.1.1.4 Incorporation of MOR-001 data into the MAA dataset

Once the MOR-001 data were assigned to MAA time points, the MOR-001 data were incorporated into the MAA flat file. MOR-001 data were combined and reshaped into the same format as the MAA data to allow appendment to the existing MAA file.

2.3.1.1.5 Incorporation of additional patient-level data as provided by clinicians

Table 18 provides a summary of the additional data provided by clinicians as a result of interviews undertaken.

Table 18: Additional data provided by clinicians

Data	Data source	Data on file†
Additional data for patients SR004-SR007	Weight and age at baseline (provided by Dr. Karolina Stepien)	Email on 03/08/2021
	EQ-5D and MPS-HAQ scores (provided by Dr. Karolina Stepien)	Email on 07/08/2021
	Additional EQ-5D and MPS-HAQ scores (provided by Dr. Karolina Stepien)	Email on 10/08/2021
	6MWT, FEV_1, FVC, MPS-HAQ	Salford MPS IVa MAA patients 07.08.2021.xlsx
Additional data for GOSH patients	Additional weight, FEV_1, FVC, 6MWT (provided by Dr. James Davison)	GOSH 20210730 JD.xlsx

Abbreviations: 6MWT, 6-minute walk test; EQ-5D, EuroQol five dimensions; FEV_1, forced expiratory volume; FVC, forced vital capacity; GOSH: Great Ormond Street Hospital; MAA, managed access agreement; MPS, mucopolysaccharidosis; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire. †Data on file documents are available from BioMarin upon request.

2.3.1.1.6 Data cleaning

The database contained several values which reflected missing values or would otherwise be considered invalid. Before any analyses were conducted, these missing or invalid values were documented and removed from the database by replacement with blank values. The variable names, the types of missing or invalid data encountered, and the action taken to address the data are shown in Table 19.

Table 19: Data cleaning audit log

Variable name	Variable description	Missing data description	Action taken
DOB	Date of birth	Missing data were coded as a value of 0	Missing records replaced with blanks
Treatment start data	MAA patients: date patients commenced treatment Ex-trial patients: date patients enrolled on MAA MOR-001 patients: date patients provided informed consent	Missing data were coded as a value of 0	Missing records replaced with blanks
Age at baseline	Age of patient at treatment start date	Missing data were coded as a value of NR	Missing records replaced with blanks
Weight	Weight in kg	Missing data were coded as values of 0, 999, 1111 and 9999	Missing records replaced with blanks
6MWT	6MWT result in metres	Missing data were coded as values of 999, 1111 and 9999. Some patients had values of zero when no test was performed.	Missing records replaced with blanks; values of zero when no test was performed replaced with blanks

Variable name	Variable description	Missing data description	Action taken
6MWT_BL	6MWT result in metres at baseline	Missing data were coded as values of 999 and 9999	Missing records replaced with blanks
Ab Titres		Missing data were coded as values of 999 and 1111	Missing records replaced with blanks
EQ-5D date	Date of EQ-5D assessment	[redacted] patients have impossible time points of [redacted] and [redacted] respectively ([redacted]).	Excluded from analysis
EQ-5D-5L_D1	Domain-level score for EQ-5D domain 1	Missing data were coded as values of 999	Missing records replaced with blanks
EQ-5D-5L_D5	Domain-level score for EQ-5D domain 5	Missing data were coded as values of 999	Missing records replaced with blanks
EQ5D_Composite	EQ-5D derived utility value	Missing data were coded as values of 999	Missing records replaced with blanks
EQ5D_BL	EQ-5D derived utility value at baseline	Missing data were coded as values of 999	Missing records replaced with blanks
EQ5D_VAS	EQ-5D visual analogue scale score	Missing data were coded as values of 999	Missing records replaced with blanks
CardiacEcho_EjectionFraction	Ejection fraction (%)	Missing data were coded as values of 999 and 9999	Missing records replaced with blanks
FEV_1_ML	Forced expiratory volume in litres	Missing data were coded as values of 999	Missing records replaced with blanks
FEV_1_ML_BL	Forced expiratory volume in litres at baseline	Missing data were coded as values of 999	Missing records replaced with blanks
FVC_ML	Forced vital capacity in litres	Missing data were coded as values of 999 and 1111	Missing records replaced with blanks
FVC_ML_BL	Forced vital capacity in litres at baseline	Missing data were coded as values of 999	Missing records replaced with blanks
MPSHAQ_Date	Date of MPS-HAQ assessment	[redacted] patients have impossible time points of [redacted] and [redacted] respectively ([redacted]).	Excluded from analysis
uKS_ugml	Urinary keratan sulfate in µg/mL	Missing data were coded as values of 999, 1111 and 9999	Missing records replaced with blanks

Variable name	Variable description	Missing data description	Action taken
uKS_ugml_BL	Urinary keratan sulfate in µg/mL at baseline	Missing data were coded as values of 999, 1111 and 9999	Missing records replaced with blanks

Abbreviations: 6MWT, 6-minute walk test; AbTitres, antibody titres; BL, baseline; DOB, date of birth; FEV_1, forced expiratory volume; FVC, forced vital capacity; MAA, managed access agreement; uKS, urinary keratan sulfate; VAS, visual analogue scale.

2.3.1.1.7 Propensity score matching

Due to time constraints, no propensity score matching (PSM) weighting was conducted. Some matching was performed based on the MorCAP1 criteria (i.e., the MAA inclusion criteria applied to the MOR-001 cohort). The definition used for the MorCAP1 population was as follows:

- MorCAP1: patients in the MOR-001 population who are ≥ 5 years of age and have a 6MWT of >30 metres and ≤ 325 metres at baseline

All analyses conducted using the MOR-001 data were performed using the MorCAP1 subpopulation. No analyses using the entire MOR-001 population were conducted.

2.3.1.1.8 Imputation of missing data

No imputation of missing data was performed. The high number of missing values and the fact that data were not missing at random limited the perceived effectiveness of any missing data handling method; time constraints were also a limiting factor.

2.3.1.1.9 Definitions of complete cases

The number of patients with complete cases across all outcomes of interest were investigated in order to conduct analyses which reflected the requests of the ERG. Six main outcomes of interest were identified:

- 6MWT
- European Quality of Life-Five Dimension-Five Level (EQ-5D-5L)
- FVC
- FEV_1
- Urinary keratin sulfate (uKS)
- Wheelchair status

The number of complete cases (i.e., patients with outcomes available at baseline, Year 1 and Year 2) for these outcomes is shown below in Table 20.

Table 20: Number of complete cases across six key outcomes in MAA patients

Timepoint	Number of complete cases		
	Treatment-naïve	Ex-trial	MAA
Year 1	6	2	8
Year 2	4	2	6
Year 3	0	0	0
Year 4	0	0	0

Abbreviations: MAA, managed access agreement.

Due to the lack of complete cases across all outcomes of interest, it was decided that complete cases would be determined on a per-outcome basis. When an analysis required more than one variable to be examined simultaneously, patients had to have complete cases in both outcomes to be considered.

2.3.1.1.10 Populations included in analyses

Four main populations were included in analyses. These included:

- All patients enrolled in the MAA (described as MAA, all)
- Ex-trial MAA patients (described as MAA, ex-trial)
- Treatment-naïve MAA patients (described as MAA, treatment-naïve)
- The MorCAP1 subpopulation of the MOR-001 study (described as MorCAP1)

2.3.1.2 Statistical analyses

Pairwise Student's T-tests were conducted on the following variables:

- 6MWT
- FEV_1
- FVC

The tests were conducted to determine change from baseline within a population and to compare the MAA patient populations to the MorCAP1 population. No statistical tests were performed using wheelchair status outcomes or EQ-5D-5L. A linear regression analysis was also conducted to check the correlation, if any, between FVC and EQ-5D.

2.3.1.3 Baseline demographics

The baseline demographics for the patient populations used in the analysis are presented below.

2.3.1.3.1 Wheelchair status baseline demographics

Baseline demographics for wheelchair status complete cases (as defined by MPS-HAQ Q33 and Q33a) are presented in Table 21, Table 22, Table 23 and Table 24.

Table 21: Baseline demographics for all MAA patients, Year 1+2 complete cases for MPS-HAQ Q33/Q33a

Health state at baseline	n	Mean weight (kg)	Mean weight (kg), SD	Mean age	Mean age, SD	% male	% female
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire; SD, standard deviation.

Table 22: Baseline demographics for ex-trial MAA patients, Year 1+2 complete cases for MPS-HAQ Q33/Q33a

Health state at baseline	n	Mean weight (kg)	Mean weight (kg), SD	Mean age	Mean age, SD	% male	% female
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire; SD, standard deviation.

Table 23: Baseline demographics for treatment-naïve MAA patients, Year 1+2 complete cases for MPS-HAQ Q33/Q33a

Health state at baseline	n	Mean weight (kg)	Mean weight (kg), SD	Mean age	Mean age, SD	% male	% female
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire; SD, standard deviation.

Table 24: Baseline demographics for MorCAP1 patients, Year 1+2 complete cases for MPS-HAQ Q33/Q33a

Health state at baseline	n	Mean weight (kg)	Mean weight (kg), SD	Mean age	Mean age, SD	% male	% female
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MPS-HAQ, mucopolysaccharidosis health assessment questionnaire; N/A, not applicable; SD, standard deviation.

2.3.1.3.2 6MWT baseline demographics

Baseline demographics for 6MWT Year 1+2 complete cases are shown below in Table 25, Table 26, Table 27, and Table 28.

Table 25: Baseline demographics for 6MWT complete cases, all MAA patients

Age group	n	% male	Mean weight (kg)	Mean weight (kg), SD
Age < 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥ 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute walk test; MAA, managed access agreement; SD, standard deviation.

Table 26: Baseline demographics for 6MWT complete cases, ex-trial MAA patients

Age group	n	% male	Mean weight (kg)	Mean weight (kg), SD
Age < 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥ 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute walk test; MAA, managed access agreement; SD, standard deviation.

Table 27: Baseline demographics for 6MWT complete cases, treatment-naive MAA patients

Age group	n	% male	Mean weight (kg)	Mean weight (kg), SD
Age < 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥ 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute walk test; MAA, managed access agreement; SD, standard deviation.

Table 28: Baseline demographics for 6MWT complete cases, MorCAP1 patients

Age group	n	% male	Mean weight (kg)	Mean weight (kg), SD
Age ≥ 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute walk test; SD, standard deviation.

2.3.1.3.3 FEV_1 baseline demographics

Baseline demographics for the FEV_1 complete case population are shown below in Table 29. All patients were at least 5 years of age as children aged less than 5 years were not eligible for lung function assessments.

Table 29: Baseline demographics for the FEV_1 complete case population

Population	n	% male	Mean weight (kg)	Mean weight (kg), SD
MAA patients, all	[redacted]	[redacted]	[redacted]	[redacted]
MAA patients, ex-trial	[redacted]	[redacted]	[redacted]	[redacted]
MAA patients, treatment-naïve	[redacted]	[redacted]	[redacted]	[redacted]
MorCAP1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abbreviations: FEV_1, forced expiratory volume; MAA, managed access agreement; SD, standard deviation.

2.3.1.3.4 FVC baseline demographics

Baseline demographics for the FEV_1 complete case population are shown below in Table 30. As for FEV_1, all patients were greater than 5 years old as children were not eligible to participate.

Table 30: Baseline demographics for the FVC complete case population

Population	n	% male	Mean weight (kg)	Mean weight (kg), SD
MAA patients, all	[redacted]	[redacted]	[redacted]	[redacted]
MAA patients, ex-trial	[redacted]	[redacted]	[redacted]	[redacted]
MAA patients, treatment-naïve	[redacted]	[redacted]	[redacted]	[redacted]
MorCAP1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; SD, standard deviation.

2.3.1.3.5 EQ-5D-5L baseline demographics

Baseline demographics for EQ-5D-5L complete cases stratified by wheelchair status are presented in Table 31, Table 32, and Table 33.

Table 31: EQ-5D complete case baseline demographics: all MAA patients

Wheelchair status	n	% male	Mean weight (kg)	Mean weight (kg), SD
Pooled	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
No use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
Some use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol five dimensions; MAA, managed access agreement; SD, standard deviation.

Table 32: EQ-5D complete case baseline demographics: ex-trial MAA patients

Wheelchair status	n	% male	Mean weight (kg)	Mean weight (kg), SD
Pooled	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
No use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
Some use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol five dimensions; MAA, managed access agreement; SD, standard deviation.

Table 33: EQ-5D complete case baseline demographics: treatment-naive MAA patients

Wheelchair status	n	% male	Mean weight (kg)	Mean weight (kg), SD
Pooled	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
No use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
Some use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol five dimensions; MAA, managed access agreement; SD, standard deviation.

2.3.2 Results

The results below detail all analyses which were conducted to update the cost-effectiveness model. For parsimony, only analyses which were incorporated into the model are presented.

2.3.2.1 Wheelchair status transition matrices

2.3.2.1.1 Baseline to Year 1

Transition matrices for baseline to Year 1 are shown below in Table 34, Table 35, Table 36, and Table 37.

Table 34: Transition matrices for baseline to Year 1, Year 1+2 complete cases, MAA patients, all

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]	[redacted]		[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair		[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 35: Transition matrices for baseline to Year 1, Year 1+2 complete cases, MAA patients, ex-trial

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]			[redacted]
Some wheelchair use		[redacted]		[redacted]
Always use wheelchair		[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 36: Transition matrices for baseline to Year 1, Year 1+2 complete cases, MAA patients, treatment-naive

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]	[redacted]		[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair			[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 37: Transition matrices for baseline to Year 1, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use			[redacted]	[redacted]
Some wheelchair use		[redacted]		[redacted]
Always use wheelchair				

2.3.2.1.2 Year 1 to Year 2

Transition matrices for Year 1 to Year 2 are shown below in Table 38, Table 39, Table 40, and Table 41.

Table 38: Transition matrices for Year 1 to Year 2, Year 1+2 complete cases, MAA patients, all

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair		[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 39: Transition matrices for Year 1 to Year 2, Year 1+2 complete cases, MAA patients, ex-trial

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]		[redacted]	[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair			[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 40: Transition matrices for Year 1 to Year 2, Year 1+2 complete cases, MAA patients, treatment-naive

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair		[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 41: Transition matrices for Year 1 to Year 2, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use				
Some wheelchair use		[redacted]		[redacted]
Always use wheelchair		[redacted]	[redacted]	[redacted]

2.3.2.1.3 Baseline to Year 2

Transition matrices for Year 1 to Year 2 are shown below in Table 42, Table 43, Table 44, and Table 45.

Table 42: Transition matrices for baseline to Year 2, Year 1+2 complete cases, MAA patients, all

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair		[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 43: Transition matrices for baseline to Year 2, Year 1+2 complete cases, MAA patients, ex-trial

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]		[redacted]	[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair		[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 44: Transition matrices for baseline to Year 2, Year 1+2 complete cases, MAA patients, treatment-naive

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use		[redacted]	[redacted]	[redacted]
Always use wheelchair			[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 45: Transition matrices for baseline to Year 2, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total
No wheelchair use		[redacted]	[redacted]	[redacted]
Some wheelchair use		[redacted]		[redacted]
Always use wheelchair				

2.3.2.2 Average annual change in 6MWT (MorCAP1 only)

6MWT scores by health state for MorCAP1 patients are shown below in Table 46. Mean changes from baseline in 6MWT test results are shown in Table 47.

Table 46: Annual change in 6WMT, Year 1+2 complete cases, MorCAP1 patients

Health state at baseline	Mean 6MWT	6MWT, SD	n
	Baseline		
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]
	12 months		
No wheelchair use			
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]
	24 months		
No wheelchair use			
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair			
Pooled	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute-walk test; N/A, not applicable; SD, standard deviation.

Table 47: Mean change from baseline in 6MWT, Year 1+2 complete cases, MorCAP1 patients

Health state	Baseline to 12 months	Baseline to 24 months
No wheelchair use	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]
Pooled	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute-walk test; N/A, not applicable.

2.3.2.3 Mean 6MWT by wheelchair status (MorCAP1 only)

Mean 6MWT scores by wheelchair status at baseline, Year 1 and Year 2 are shown in Table 48; as data from three time points were pooled, there are 27 data points available from a sample size of 9 patients.

Table 48: Mean 6MWT by wheelchair status, Year 1+2 complete cases, MorCAP1 patients

Health state	Mean 6MWT	6MWT, SD	n
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute-walk test; N/A, not applicable.

2.3.2.4 6MWT values at which patients transition to increased wheelchair dependency health states (MorCAP1)

6MWT values for when patients transitioned to alternative health states were estimated by generating transition matrices and calculating the mean 6MWT value for each cell in the matrices. Transitions to a worse health state are red; transitions to an improved health state are green. Patients included in this analysis were complete cases for both 6MWT and wheelchair status. Results are shown in Table 49, Table 50, and Table 51; blank cells indicate that no patients made the transition indicated.

Table 49: 6MWT scores associated with each transition, baseline to Year 1, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use		Some wheelchair use		Always use wheelchair		Total *(n)*
	n	6MWT	n	6MWT	n	6MWT	
No wheelchair use					[redacted]	[redacted]	[redacted]
Some wheelchair use			[redacted]	[redacted]			[redacted]
Always use wheelchair							[redacted]

Abbreviations: 6MWT, 6-minute-walk test.

Table 50: 6MWT scores associated with each transition, Year 1 to Year 2, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use		Some wheelchair use		Always use wheelchair		Total *(n)*
	n	6MWT	n	6MWT	n	6MWT	
No wheelchair use							[redacted]
Some wheelchair use			[redacted]	[redacted]			[redacted]
Always use wheelchair			[redacted]	[redacted]			[redacted]

Abbreviations: 6MWT, 6-minute-walk test.

Table 51: 6MWT scores associated with each transition, baseline to Year 2, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use		Some wheelchair use		Always use wheelchair		Total *(n)*
	n	6MWT	n	6MWT	n	6MWT	
No wheelchair use			[redacted]	[redacted]			[redacted]
Some wheelchair use			[redacted]	[redacted]			[redacted]
Always use wheelchair							[redacted]

Abbreviations: 6MWT, 6-minute-walk test.

2.3.2.5 Mean change in 6MWT from baseline (MAA)

The mean change in 6MWT scores from baseline are shown below in Table 52, Table 53 and Table 54.

Table 52: Mean change in 6MWT from baseline, Year 1+2 complete cases, MAA patients, all

Timepoint	n	Mean 6MWT	6MWT, SD	Change from BL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute-walk test; BL, baseline; MAA, managed access agreement; N/A, not applicable; SD, standard deviation.

Table 53: Mean change in 6MWT from baseline, Year 1+2 complete cases, MAA patients, ex-trial patients

Timepoint	n	Mean 6MWT	6MWT, SD	Change from BL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute-walk test; BL, baseline; MAA, managed access agreement; N/A, not applicable; SD, standard deviation.

Table 54: Mean change in 6MWT from baseline, Year 1+2 complete cases, MAA patients, treatment-naïve patients

Timepoint	n	Mean 6MWT	6MWT, SD	Change from BL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute-walk test; BL, baseline; MAA, managed access agreement; N/A, not applicable; SD, standard deviation.

2.3.2.6 Mean FVC for patients entering "wheelchair dependent" health state

FVC scores based on patient wheelchair status transitions were calculated using the same methods as for 6MWT scores; results are shown in Table 55, Table 56, and Table 57.

Table 55: FVC values associated with each transition, baseline to Year 1, Year 1+2 complete cases, MorCAP1 patients

	No wheelchair use		Some wheelchair use		Always use wheelchair		
FROM ↓ TO →	n	FVC	n	FVC	n	FVC	Total *(n)*
No wheelchair use					[redacted]	[redacted]	[redacted]
Some wheelchair use			[redacted]	[redacted]			[redacted]
Always use wheelchair							[redacted]

Abbreviations: FVC, forced vital capacity.

Table 56: FVC values associated with each transition, Year 1 to Year 2, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use		Some wheelchair use		Always use wheelchair		Total *(n)*
	n	FVC	n	FVC	n	FVC	
No wheelchair use							0
Some wheelchair use			[redacted]	[redacted]			7
Always use wheelchair					[redacted]	[redacted]	1

Abbreviations: FVC, forced vital capacity.

Table 57: FVC values associated with each transition, baseline to Year 2, Year 1+2 complete cases, MorCAP1 patients

FROM ↓ TO →	No wheelchair use		Some wheelchair use		Always use wheelchair	
	n	FVC	*n*	FVC	*n*	FVC
No wheelchair use					[redacted]	[redacted]
Some wheelchair use			[redacted]	[redacted]		
Always use wheelchair						

Abbreviations: FVC, forced vital capacity.

2.3.2.7 Mean annual change in FVC by wheelchair status

Mean change in FVC by wheelchair status is shown below in Table 58, Table 59, Table 60, and Table 61.

Table 58: Mean annual change in FVC by health status, Year 1 and 2 complete cases, Year 1+2 complete cases, MAA patients, all

Timepoint	*n*	Mean FVC	FVC, SD	Change from BL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; FVC, forced vital capacity; MAA, managed access agreement; N/A, not applicable; SD, standard deviation.

Table 59: Mean annual change in FVC by health status, Year 1 and 2 complete cases, Year 1+2 complete cases, MAA patients, ex-trial

Timepoint	*n*	Mean FVC	FVC, SD	Change from BL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; FVC, forced vital capacity; MAA, managed access agreement; N/A, not applicable; SD, standard deviation.

Table 60: Mean annual change in FVC by health status, Year 1 and 2 complete cases, Year 1+2 complete cases, MAA patients, treatment-naive

Timepoint	*n*	Mean FVC	FVC, SD	Change from BL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; FVC, forced vital capacity; MAA, managed access agreement; N/A, not applicable; SD, standard deviation.

Table 61: Mean annual change in FVC by health status, Year 1 and 2 complete cases, Year 1+2 complete cases, MorCAP1 patients

Timepoint	*n*	Mean FVC	FVC, SD	Change from BL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; FVC, forced vital capacity; N/A, not applicable; SD, standard deviation.

2.3.2.8 Mean change in FVC within health states (MorCAP1 only)

FVC values by health state for MorCAP1 patients are shown below in Table 62. Mean changes from baseline in FVC test results are shown in Table 63.

Table 62: Annual change in FVC, Year 1+2 complete cases, MorCAP1 patients

Health state at baseline	Baseline		
	Mean FVC	FVC, SD	n
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]
	12 months		
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]
	24 months		
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]

Abbreviations: FVC, forced vital capacity; N/A, not applicable; SD, standard deviation.

Table 63: Mean change from baseline in FVC, Year 1+2 complete cases, MorCAP1 patients

Health state	Baseline to 12 months	Baseline to 24 months
No wheelchair use	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]
Pooled	[redacted]	[redacted]

Abbreviations: FVC, forced vital capacity.

2.3.2.9 Mean increase in EQ-5D-5L for each 1-litre increase in FVC (MAA)

The relationship between EQ-5D-5L and FVC was investigated to determine whether a correlation could be established between these variables. EQ-5D-5L scores were plotted against their corresponding FVC scores at baseline, 12 months and 24 months as shown in [redacted]. A total of 48 patients in the MAA dataset were complete cases for both EQ-5D and FVC. No correlation between EQ-5D-5L and FVC was observed by visual inspection; this was not investigated statistically.

[redacted]

Abbreviations: EQ-5D-5L, EuroQol five dimensions five levels; FVC, forced vital capacity.

2.3.2.10 EQ-5D-5L by health status

EQ-5D-5L composite utility values were generated for all observations across wheelchair states; three times the observations were available as there were complete cases (complete cases multiplied by the number of observations per case).

Table 64: EQ-5D-5L scores by wheelchair status, Year 1+2 complete cases, MAA patients, all

Health state	EQ-5D-5L, mean	EQ-5D-5L, SD	n
Pooled	[redacted]	[redacted]	[redacted]
No use wheelchair	[redacted]	[redacted]	[redacted]
Some use wheelchair	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L, EuroQol five dimensions five levels; MAA, managed access agreement; SD, standard deviation.

Table 65: EQ-5D-5L scores by wheelchair status, Year 1+2 complete cases, MAA patients, ex-trial

Health state	EQ-5D-5L, mean	EQ-5D-5L, SD	n
Pooled	[redacted]	[redacted]	[redacted]
No use wheelchair	[redacted]	[redacted]	[redacted]
Some use wheelchair	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L, EuroQol five dimensions five levels; MAA, managed access agreement; SD, standard deviation.

Table 66: EQ-5D-5L scores by wheelchair status, Year 1+2 complete cases, MAA patients, treatment-naive

Health state	EQ-5D-5L, mean	EQ-5D-5L, SD	n
Pooled	[redacted]	[redacted]	[redacted]
No use wheelchair	[redacted]	[redacted]	[redacted]
Some use wheelchair	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L, EuroQol five dimensions five levels; MAA, managed access agreement; SD, standard deviation.

2.3.2.11 Treatment response status at 2 years

Patients were defined as either “long-term stabilisers” or “mild decliners” based on the following criteria:

- Long-term responders: patients whose 24-month 6MWT result was greater than or equal to their 6MWT result at baseline
- Mild decliners: patients whose 24-month 6MWT result did not equal or exceed their baseline 6MWT score

Response categories for each patient population are shown below in Table 67, Table 68, Table 69, and Table 70.

Table 67: Response status, Year 1+2 complete cases, MAA patients, all

Outcome	n	Long term stabilisers	Mild decliners
n	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 68: Response status, Year 1+2 complete cases, MAA patients, ex-trial

Outcome	n	Long term stabilisers	Mild decliners
n	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 69: Response status, Year 1+2 complete cases, MAA patients, treatment-naïve

Outcome	n	Long term stabilisers	Mild decliners
n	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement.

Table 70: Response status, Year 1+2 complete cases, MorCAP1 patients

Outcome	Value	Long term stabilisers	Mild decliners
n	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]

2.3.3 Supplementary statistical analyses

Pairwise Student's T-tests were conducted to determine whether changes from baseline and differences between patient populations were statistically significant.

2.3.3.1 6MWT

2.3.3.1.1 Change from baseline

Table 71: T-test results for 6MWT change from baseline, Year 1+2 complete cases, MAA patients, all

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-1.498377	0.1389994	0.05	n.s.
24 months	-1.4169552	0.1612022	0.05	n.s.

Abbreviations: 6MWT, 6-minute-walk test; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 72: T-test results for 6MWT change from baseline, Year 1+2 complete cases, MAA patients, ex-trial

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.1429773	0.8873201	0.05	n.s.
24 months	-0.4764316	0.6372376	0.05	n.s.

Abbreviations: 6MWT, 6-minute-walk test; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 73: T-test results for 6MWT change from baseline, Year 1+2 complete cases, MAA patients, treatment-naive

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-1.77676787	0.08473207	0.05	n.s.
24 months	-1.4516232	0.1557949	0.05	n.s.

Abbreviations: 6MWT, 6-minute-walk test; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 74: T-test results for 6MWT change from baseline, Year 1+2 complete cases, MorCAP1 patients

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.575339	0.569371	0.05	n.s.
24 months	-0.4850548	0.6311243	0.05	n.s.

Abbreviations: 6MWT, 6-minute-walk test; n.s., not significant; N/A, not applicable.

2.3.3.1.2 MAA vs MorCAP1

Pairwise comparisons for the MAA populations versus the same timepoint for the MorCAP1 analyses are shown below in Table 75, Table 76, and Table 77.

Table 75: T-test results for 6MWT scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, all

Timepoint	t statistic	p-value	alpha	significance
Baseline	-0.3336476	0.7403971	0.05	n.s.
12 months	-0.8231287	0.4178456	0.05	n.s.
24 months	-0.9365229	0.3561403	0.05	n.s.

Abbreviations: 6MWT, 6-minute-walk test; MAA, managed access agreement; n.s., not significant.

Table 76: T-test results for 6MWT scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, ex-trial

Timepoint	t statistic	p-value	alpha	significance
Baseline	-1.1218008	0.2708726	0.05	n.s.
12 months	-0.6190597	0.5408439	0.05	n.s.
24 months	-0.9853018	0.3321092	0.05	n.s.

Abbreviations: 6MWT, 6-minute-walk test; MAA, managed access agreement; n.s., not significant.

Table 77: T-test results for 6MWT scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, treatment-naive

Timepoint	t statistic	p-value	alpha	significance
Baseline	0.416733	0.6797245	0.05	n.s.
12 months	-0.8373273	0.4086035	0.05	n.s.
24 months	-0.6522643	0.5187579	0.05	n.s.

Abbreviations: 6MWT, 6-minute-walk test; MAA, managed access agreement; n.s., not significant.

2.3.3.2 FEV_1

2.3.3.2.1 Change from baseline

Table 78: T-test results for FEV_1 change from baseline, Year 1+2 complete cases, MAA patients, all

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.4525081	0.6537934	0.05	n.s.
24 months	-0.4663191	0.6439675	0.05	n.s.

Abbreviations: FEV_1, forced expiratory volume; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 79: T-test results for FEV_1 change from baseline, Year 1+2 complete cases, MAA patients, ex-trial

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-1.58442574	0.14273264	0.05	n.s.
24 months	-1.3544924	0.2093117	0.05	n.s.

Abbreviations: FEV_1, forced expiratory volume; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 80: T-test results for FEV_1 change from baseline, Year 1+2 complete cases, MAA patients, treatment-naive

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.2335561	0.8177185	0.05	n.s.
24 months	-0.2361512	0.8157321	0.05	n.s.

Abbreviations: FEV_1, forced expiratory volume; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 81: T-test results for FEV_1 change from baseline, Year 1+2 complete cases, MorCAP1 patients

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.1263189	0.9006269	0.05	n.s.
24 months	-0.2384541	0.8137406	0.05	n.s.

Abbreviations: FEV_1, forced expiratory volume; n.s., not significant; N/A, not applicable.

2.3.3.2.2 MAA vs MorCAP1

Table 82: T-test results for FEV_1 scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, all

Timepoint	t statistic	p-value	alpha	significance
Baseline	2.02685658	0.05541844	0.05	n.s.
12 months	1.86417875	0.07700177	0.05	n.s.
24 months	1.90505832	0.07143065	0.05	n.s.

Abbreviations: FEV_1, forced expiratory volume; MAA, managed access agreement; n.s., not significant.

Table 83: T-test results for FEV_1 scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, ex-trial

Timepoint	t statistic	p-value	alpha	significance
Baseline	3.630299552	0.003519113	0.05	***
12 months	3.187984139	0.007239638	0.05	***
24 months	3.075931752	0.008292197	0.05	***

*** p<0.001
Abbreviations: FEV_1, forced expiratory volume; MAA, managed access agreement.

Table 84: T-test results for FEV_1 scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, treatment-naive

Timepoint	t statistic	p-value	alpha	significance
Baseline	1.1439091	0.265787	0.05	n.s.
12 months	1.074355	0.2949028	0.05	n.s.
24 months	1.1474616	0.2641148	0.05	n.s.

Abbreviations: FEV_1, forced expiratory volume; MAA, managed access agreement; n.s., not significant.

2.3.3.3 FVC

2.3.3.3.1 Change from baseline

Table 85: T-test results for FVC change from baseline, Year 1+2 complete cases, MAA patients, all

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.2994291	0.7666859	0.05	n.s.
24 months	-0.3628652	0.7193055	0.05	n.s.

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 86: T-test results for FVC change from baseline, Year 1+2 complete cases, MAA patients, ex-trial

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-1.6872117	0.1614096	0.05	n.s.
24 months	-1.780283	0.1455038	0.05	n.s.

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 87: T-test results for FVC change from baseline, Year 1+2 complete cases, MAA patients, treatment-naive

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.1257641	0.9011788	0.05	n.s.
24 months	-0.1417326	0.8887408	0.05	n.s.

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 88: T-test results for FVC change from baseline, Year 1+2 complete cases, MAA patients, MorCAP1

Timepoint	t statistic	p-value	alpha	significance
Baseline	N/A	N/A	0.05	n.s.
12 months	-0.03705283	0.97077784	0.05	n.s.
24 months	-0.1510495	0.8813194	0.05	n.s.

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

2.3.3.3.2 MAA vs MorCAP1

Table 89: T-test results for FVC scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, all

Timepoint	t statistic	p-value	alpha	significance
Baseline	2.2124418	0.038271	0.05	*
12 months	1.89739748	0.07175113	0.05	n.s.
24 months	2.01213005	0.05838632	0.05	n.s.

* p<0.05

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

Table 90: T-test results for FVC scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, ex-trial

Timepoint	t statistic	p-value	alpha	significance
Baseline	3.905663423	0.002404763	0.05	***
12 months	3.026871137	0.009582528	0.05	***
24 months	2.95654501	0.01062512	0.05	*

* p<0.05; *** p<0.001

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; N/A, not applicable.

Table 91: T-test results for FVC scores versus MorCAP1 value at same timepoint, Year 1+2 complete cases, MAA patients, treatment-naive

Timepoint	t statistic	p-value	alpha	significance
Baseline	1.553	0.1353654	0.05	n.s.
12 months	1.3550097	0.189846	0.05	n.s.
24 months	3.06681575	0.00938968	0.05	***

*** p<0.001

Abbreviations: FVC, forced vital capacity; MAA, managed access agreement; n.s., not significant; N/A, not applicable.

2.3.4 Discussion

2.3.4.1 Limitations

The analysis had several key limitations:

- Complete case analyses introduced an inherent bias into the results:
    - The complete case analyses resulted in a small sample size for many outcomes
    - Large numbers of patient records were discarded due to being incomplete

- Heterogeneity between the baseline statistics of the MAA population and the MorCAP1 population

2.3.4.1.1 Complete case analysis limitations

The complete case analysis allowed for the sojourns of individuals to be tracked but also resulted in many results being discarded due to incomplete data. This was addressed in part by conducting the analysis on a per-outcome basis, i.e., a patient could be defined as a complete case for a given outcome if they had data available at all follow-up timepoints of interest (i.e., 12 months and 24 months) for that outcome alone. Another limitation of the complete case approach was that cases were not missing at random and there may have been systematic reasons for why certain outcomes were not captured at given timepoints. This is likely to mean that patients who have complete cases are different to those who did not have complete cases.

The missingness of data was also high; of 63 patients who were on-treatment in the MAA population, only 34 patients were complete cases for 6MWT up to two years; of the 353 MOR-001 patients, only 17 were complete cases for 6MWT after the MorCAP1 inclusion criteria were applied.

Data imputation methods may have gone some way to address missing values; however, these were not conducted due to the high number of missing values and the limited time available.

2.3.4.1.2 Heterogeneity

The pairwise T-tests showed significant differences ($p<0.05$) between the treatment-naïve MAA patients and the MorCAP1 population at baseline for FEV_1 and FVC outcomes (Table 90) which suggests that any comparison should be made with caution as the populations appeared to be different at baseline. This may have been addressed by a propensity score matching analysis; however, it was not possible to complete a PSM analysis due to time constraints. The PSM analysis would also have been limited by the number of patients available due to the complete case approach. Use of the MorCAP1 population was intended to at least partially address the heterogeneity issues which were likely to arise by applying the selection criteria for entry into the MAA to the population of the MOR-001 study.

2.4 Clinical value story for elosulfase alfa: Company cornerstone statements

The data presented in this report (Section 2.3) suggests numerical differences from baseline to Years 1 and 2 for the specific clinical outcomes of interest for patients receiving elosulfase alfa; however, analyses have demonstrated that these numerical differences are not statistically significant. This is likely attributable to the low patient numbers available due to the complete case analysis approach that was taken.

Despite the lack of statistically significant differences in clinical outcomes from baseline to Years 1 and 2, based on expert clinical opinion gleaned from advisory boards conducted by the Company, clinical experience suggests that there are clinically important differences observed in the outcomes of interest in patients receiving elosulfase alfa. The Company conducted a clinical story virtual workshop, which included four Consultant clinicians with expertise in metabolic disorders based in the UK with substantial experience treating adult and paediatric patients with MPS IVa. Clinician opinion was that compared with before treatment or no treatment, in patients receiving elosulfase alfa there was:

- A sustained improvement in 6MWT over time
- An improvement and stabilisation of lung function
- Sustained growth in paediatric patients
- A movement away from wheelchair dependency to patient choice as to when their wheelchair was used
- Increased independent functioning
- A reduction in pain medication/analgesic use in adult patients
- An increase in the number of surgeries being performed due to paediatric patients being better candidates for surgery as a result of receiving elosulfase alfa

These observations are corroborated by several example patient case studies in adult and paediatric patients, presented in Section 2.5.

2.5 Patient case studies[a]

MPS IVa is a genetic metabolic disorder in which patients inherit mutations in both copies of the GALNS gene. A molecular analysis of 163 patients with MPS IVa identified 99 different mutations of the GALNS genes and 26 single nucleotide polymorphisms, which may by associated with the disease (13). Given the wide genetic variability underlying MPS IVa, the clinical manifestation of the disease is highly heterogenous across patients. For example, patients may range from the classical presentation with deformity of the chest, a height of approximately 1 m and dependence on a wheelchair, to non-classical patients with a height of approximately 1.5 m and the ability to walk independently, but with a history of spinal surgeries and restrictive pulmonary disease. Disease heterogeneity means that, when untreated, patients are destined for certain outcomes across the spectrum of disease severity.

Heterogeneity in residual disease burden may also have a substantial impact on the extent to which patients experience the benefits of elosulfase alfa. For example, disease variants are responsible for causing severe disease phenotypes; a common example of which is the Saleh Khana variant, which is common to the Midlands, in particular Birmingham. One clinician noted that approximately 20% of their patients with more severe forms of disease, discontinued enzyme replacement therapy (ERT) due to disease progression which resulted in the burden of receiving treatment no longer being manageable. However, in contrast, a second clinician stated that they had observed a much higher success rate in paediatric patients, with only one out of 17 patients discontinuing treatment, as a result of a perceived lack of benefit (see section 0 for further details on the benefits of elosulfase alfa in paediatric patients).

Overall, heterogeneity in the genetic basis and natural history of MPS IVa can lead to substantial differences in response to treatment, ranging from improvements in energy levels which can be maintained for 6–8 weeks following cessation in treatment, to no longer requiring the use of a hoist for their bed, toilet, and bath. When combined with the rarity of the disease, heterogeneity can make it challenging to draw conclusions regarding the optimal management of patients, and there is a need to draw on expert clinical experience to develop guidance (14). Reports from clinicians indicate that improvement is seen when observing patients on an individual basis, including improvements in their ability to carry out simple everyday tasks that may be missed by clinical trials. The following patient cases provide specific, relevant examples of treatment outcomes that may not be captured in the trial data but may be of particular importance to patients' quality of life.

2.5.1 Benefits of treatment in an immobile patient – Patient 1

[redacted]

[a] Please note that patient numbers used in this report (e.g., Patient 1) do not correspond to the patient identification (PID) numbers in the corresponding data flat file described in Section 2.3 (Clinical efficacy data).

[redacted]

[redacted]

[redacted]

2.5.2 Benefits of treatment in a highly active patient – Patient 2

[redacted]

[redacted]

2.5.3 Benefits of treatment in a non-classical patient – Patient 3

[redacted]

[redacted]

[redacted]

2.5.4 Benefits of treatment in children

[redacted]

[redacted]

2.5.5 Summary

Overall, clinicians reported that they observed a general improvement in clinical and treatment outcomes following initiation of therapy compared with prior to therapy. However, clinicians also emphasised additional benefits such as a reduction in the need for pain medication, increased energy levels, improvements in the ability to accomplish everyday tasks, and patients gaining the confidence to embark on further education or to take on new/existing hobbies. These reports from clinicians underscore the heterogeneity in patient's experience of MPS IVa and the benefits gained from elosulfase alfa, highlighting the need to consider individual patient experiences that support, and go beyond, the benefits captured by the clinical trial data.

3 Economic section

3.1 Results – All MAA population

Table 92: Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosufase alfa	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 93: Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosufase alfa	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

[redacted]

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

3.2 Results – Treatment-naïve population

Table 94: Discounted results

	Total			Incremental			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosufase alfa	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 95: Undiscounted results

	Total			Incremental			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elosufase alfa	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

[redacted]

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

4 Conclusions

The data presented in this report demonstrated that numerical differences were observed from baseline to Years 1 and 2 for the clinical outcomes of interest for patients with MPS IVa receiving elosulfase alfa. Subsequent analyses demonstrated that while these differences were not statistically significant, this was likely attributable to the low patient numbers available due to the complete case analysis approach that was taken.

Despite this, expert clinical opinion was that in clinical practice, compared with before treatment or no treatment, patients with MPS IVa receiving elosulfase alfa had a sustained improvement in 6MWT over time, an improvement and stabilisation of lung function, sustained growth, a reduced dependency on wheelchair use, increased independent functioning, a reduction in pain medication/analgesic use, and an increase in the number of surgeries being performed.

Following implementation of changes as per the ERG's requests, the ICERs were similar to the base case ICERs calculated for the original submission for the undiscounted all-MAA results (undiscounted original ICER: [redacted]; undiscounted updated ICER: [redacted]) and were approximately 11% higher for the discounted results (original ICER: [redacted]; discounted updated ICER; [redacted]).

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2)

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Tuesday 11 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with mucopolysaccharidosis type IVa and current treatment options	
About you	
1.Your name	**Katy Brown**
2. Are you (please tick all that apply):	☐ a patient with mucopolysaccharidosis type IVa? ☐ a patient with experience of the treatment being evaluated? ☒ a carer of a patient with mucopolysaccharidosis type IVa? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	The Society for Mucopolysaccharide Diseases (MPS Society)
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with mucopolysaccharidosis type IVa? If you are a carer (for someone with this condition) please share your experience of caring for them.	My eldest son, Sam has Mucopolysaccharidosis Type IVa. He is almost 13 and was diagnosed aged 17 months. I therefore have almost 12 years' worth of experience of the condition. Although I did not connect the dots at the time, there were clear signs of what I now know to be MPS IVa from 6 months of age. Sam's physical development began to lag behind other babies; he did not crawl. He could sit up if I sat him up, but he could not get up to sit up himself from lying down. Later – he could walk if we stood him up, but it took him a long time to learn how to stand up from sitting. I remember putting him at the top of a slide in the park one day. He slid down but fell back and banged his head on the slide because he could not hold his body weight and neck rigidly enough. I remember this awful feeling, knowing that what I was seeing in Sam was not what I was seeing in other children. From the point of weaning, he began to be very sick when he ate – 2 / 3 times a day sometimes. His weight gain stopped – partially from the sickness, partially because his growth had already begun to slow. As a parent, this was very

	concerning. I instinctively knew something wasn't right, but I had no idea what it was. Sam was diagnosed at 17 months, prompted by the gibbus at the base of his spine. We were referred to Royal Manchester Children's Hospital, where Sam's care continues to be managed excellently. As a toddler, it became very clear, very quickly that Sam did not trust his own body. He would not walk on grass or uneven surfaces. He was extremely guarded and cautious in everything he did. From a very young age, MPS IVa had already begun to confine him and limit his horizons. He would not try new things. He stayed in a very safe space, emotionally and physically which continues to impact his self-esteem, motivation and well-being to this day. At the same time he had begun to see hospital trips and medical interventions as normal, part of his every day life. He was hospitalised twice with pneumonia. The four / five hour round trip to Manchester became common place for him. Sam was invited to take part in the clinical trial for Elosulfase Alfa aged 3. There was absolutely no question in our minds – we absolutely wanted him to have this opportunity. This meant him being in hospital for a day a week, for over 4 years during and following the clinical trial before he had a port fitted, and treatment moved to the home. This was an enormous family commitment but we could see the benefits very quickly. The benefits to Sam since starting treatment with Elosulfase Alfa have been immense. I've detailed these in Section 9, but I can't stress strongly enough the impact it has had on his strength, stamina, physical health, well-being and quality of life. All of the impacts of the condition that I talk about below would be amplified ten-fold if he were not in receipt of this treatment. I can say that with total confidence. Aged 4, Sam had a cervical spinal fusion. This was a huge experience for him and for us. It was a traumtatic 3 months, but absolutely essential. He also had his tonsils and adenoids out and two sets of grommets. Sam took all of this in his stride

	and coped surprisingly well at the time. But these procedures have stored up psychological impacts that he continues to carry with him today. Having MPSIVa involves lots of medical interventions and lots of time away from school, home and fun stuff. As Sam has got older, the impacts of his condition on his independence has become more apparent and important. Much of this is as a result of his height and the physical challenges with some daily activities. His height excludes him from many activities and this upsets him. He is excluded (often unintentionally) from conversations with his friends because of his height difference and his inability to keep up if they are running about. Others assume he is much younger than he really is, and treat him differently, even if this is not intended. Some daily tasks are challenging for him too; taking tops of bottles, squeezing ketchup, reaching things, carrying bags and books at school. His teachers consistently say that they can see his incredible ability and his potential, but this is not always reflected in his grades because it is hard for him to get written work typed or down on paper because of his lax wrists. He rarely has issues with fatigue – because of Elosulfase Alfa – and this is critical to his success at school. In caring for a child with MPS IVa, everything requires forward thinking and planning. And even with the best of planning, sometimes things happen. For example sleeping over in the Church Hall when he was in Beavers. He got trapped in the toilets because he couldn't push the door to get out. He was devastated and terrified and it spoilt the whole experience for him. Last year, some students on the school bus were messing with the stop buttons, and so the bus driver ignored the request to stop and drove a mile past his stop. For any other child, this would be nothing more than an inconvenience, they would just walk home. Sam couldn't do this. He rang me in tears. I was at work 2 hours away. These situations have left him feeling vulnerable. Unfortunately, the world is not set up for you when you are only a metre tall. But without Elosulfase-Alfa, there is no way Sam would have the strength, stamina or confidence to be able to attempt these things independently.

	Whilst things are more difficult for Sam than they would be without Morquio, Elosulfase Alfa unlocks the door to activities and opportunities than would otherwise be totally off-limits. Sam has a younger sibling, Alex who does not have the condition. In addition to Elosulfase Alfa opening the door to activities and opportunities for Sam, it also does the same for the family unit as a whole. If Sam were not able to be out and about on evenings and at weekends because of pain or fatigue, the family's ability to socialise and do things together would be severely impaired, with a significantly detrimental impact on Alex, who already has to adjust his life and activities to accommodate Sam's needs. In addition, my husband and I would have to alter our working patterns to provide wrap-around care for Sam after school if he were not able to get to and from school independently, which would impact our jobs, our well-being and ability to provide for our family. Ultimately if Sam's mobility deteriorated significantly, we may have to consider significant, expensive alterations to our house, or even need to move house. Because Sam's condition has not worsened, this emotional and financial upheaval is not something we have had to face into. The impacts of the condition are complex and systemic and cannot be over-simplified. The root to him being his best self, physically and emotionally, is absolutely him having maximum physical strength, stamina and energy, and this requires good respiratory function, proper sleep, and minimal pain and discomfort. If all of these things are in place, in my experience, Sam can be a world-beater – independent, confident, ambitious, resilient, capable, happy. He really can do anything he puts his mind to. But in those moments where this hasn't been there, he quickly becomes a shadow of himself. And no child should be condemned to be a shadow. Our aspiration for Sam ultimately is that he is happy, fulfilled and independent. If Elosulfase Alfa were taken away, Sam's world would shrink immeasurably. He would be condemned to losing so much of what makes him who he is. That cheeky glint, that smile, the levity and the fun. The hope. He deserves far more than that.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for mucopolysaccharidosis type IVa on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	There are no current treatments other than Elosufase Alfa
8. If there are disadvantages for patients of current NHS treatments for mucopolysaccharidosis type IVa (for example how elosulfase alfa is given or taken, side effects of treatment etc) please describe these	There are no current treatments other than Elosufase Alfa
Advantages of this treatment	
9a. If there are advantages of elosulfase alfa over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	Sam has had Elosulfase Alfa for over 9 years, It has made an enormous difference to Sam's life. His stamina has definitely increased over time. He almost never suffers with fatigue, even as he has got older and the demands of school and life have increased. I say sometimes he is like an Energiser Bunny – he just keeps going. It is tricky to compare Sam's stamina and fatigue to his pre-Elosulfase Alfa days as he was so young, but based on what I understand the natural progression of the disease to be, Sam's energy is exemplary. Fundamentally this means that the impacts of his health condition are minimised in his day to day life. I've heard stories of other Morquio patients who have to go to bed immediately after school because they are so exhausted. This has never been the case for Sam and the

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	benefit this has on his quality of life is immeasurable. He can be his best at school, and still have the energy for socialising or relaxing with friends and family. Sam suffers with almost no pain. If he's done a lot of exercise during the day, his joints ache whilst walking, but on a "normal" day, pain is of no concern whatsoever. I understand this to be very unusual for Morquio patients and I strongly believe the impact of Elosulfase Alfa here is critical. Physically his abilities have not deteriorated as he has got older. He can still walk a good distance independently (his walk tests are 300 metres + and have been over 400 metres at times over the last 5 years). Last year, we collectively ran and walked a marathon as a family around our garden whilst shielding through lockdown. Sam took a full and active part, running the last couple of laps. Pre-lockdown, Sam was coming home from school on the bus on his own two days a week, walking a good 500 metres from the bus stop home, carrying his own bag. He was getting into the house independently and taking care of himself for an hour until we came home from work. He is almost totally independent with his personal care, only requiring help with fiddly top buttons and shoe laces. Again, the impact on his quality of life, well-being and independence in being physically able to do this is immeasurable. We are about to get a wheelchair for Sam, but the driver to get this has been independence and not pure mobility. Rise and fall will help him to access things independently at school, talk and socialise on a level with his friends and to help him to move around school whilst carrying books and equipment. His lung function has improved substantially over the past few years. He has not had a chest infection for 7 years. This again is critical in him remaining independent, fit and healthy. At a young age, Sam had mild / moderate hearing loss and twice had grommets fitted. Since the last grommets came out (over 5 years ago), Sam's hearing has been consistently good with no need for further procedures or hearing aids. 5 years ago, Sam had an 8 week hiatus in treatment when this was withdrawn.

	During this period, corneal clouding appeared for the first time ever. Once treatment re-started, the corneal clouding stabilised and has never increased since. Through that 8 week period that his treatment stopped, his movement (within 3-4 weeks) become noticeably stiffer and more laboured. Once treatment started again, this reversed. This for more was total proof of the benefits Elosulfase Alfa has for him. I am in contact with other parents of children with Morquio Syndrome, and my views are consistent with their experiences. I have also spoken to adults who began treatment for the first time, and the benefits they have seen are remarkable. As previously stated, the impacts of the condition, and the treatment should not be over-simplified. The treatment substantially improves a number of different factors – his health, respiratory health, pain, strength and stamina. These are the building blocks that need to be in place for a substantially improved quality of life, and Elosulfase Alfa absolutely secures those building blocks for Sam, and has done for almost a decade. Sam is an extremely intelligent boy, with huge potentially academically and otherwise. But there is no way that he can fulfil this potential if he is fatigued and in constant pain. Elosulfase Alfa substantially increases the chances of him living an independent life in the future – both in terms of physically independence and financial independence. Elosulfase Alfa absolutely gives him the ability to maximise his potential and be the best he can be. Those 8 vials allow him to be his whole self - to hope, dream, aspire and LIVE. Something that we all sometimes take for granted if we aren't unfortunate enough to be born with a life limiting condition. When making your decision in June, I challenge you to explain your decision directly to Sam. A 12 year old boy who has already faced more challenges in his life than most of us could imagine. A young man have gave up a week a day for 4 years to be part of a clinical trial. My son who is prepared to go through an intrusive weekly infusion because he knows how much it benefits him. If you can't find a way to explain it to him, then you've made the wrong choice.

Disadvantages of this treatment	
10. If there are disadvantages of elosulfase over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	The weekly infusion process can be intrusive and time consuming (4 hours end to end). Sam has a port and I now administer his infusions, which makes this less intrusive to his life and schoolwork than it used to be when he was travelling to Manchester every week. At the end of the day, this is not just popping a pill; a weekly infusion involves a significant commitment and disruption to daily life, as well it being physically intrusive. Yet it is absolutely worth it. If we did not see the benefits of Elosulfase Alfa, quite frankly, we would not do it and we would not put Sam through it every single week. I am aware that some patients have had reactions to the treatment, but bar a mild temperature, this has never been the case for Sam.
Patient population	
11. Are there any groups of patients who might benefit more from elosulfase alfa or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The earlier a patient could receive Elosulfase Alfa, the better. Sam received it from the age of 3, but if it had been earlier, earlier damage to his body could have been reduced or stopped. However, adults and teenagers I know who started treatment at a much older age have seen significant improvements as well. I do not think any specific group of patients would benefit less from the treatment, unless there were a medical reason for this (e.g. antibody reactions)

Equality	
12. Are there any potential equality issues that should be taken into account when considering mucopolysaccharidosis type IVa and elosulfase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	All Morquio patients fall under the protected characteristic of disability. As an ultra-rare condition with less than 70 patients in England, there is structural discrimination which puts patients at a disadvantage when it comes to the reimbursement of treatment, for the following reasons: **Cost** The significant cost of therapies like Elosulfase Alfa is primarily as a result of the very low number of patients across which significant R&D costs can be recovered. This is a structural factor which is entirely beyond the control of the patient and occurs for no other reason than because the disease is so rare. However there is no adjustment in the Cost per QALY hurdle to take account of this structural factor and therefore the process is completely discriminatory to anyone with an ultra-rare condition. **Benefits** Because of the significantly low numbers of patients affected by MPS IVa, it is difficult, if not impossible sometimes to achieve the same level of data collection as would be expected with a condition that impacts far more people. • Natural history studies are more limited and so the comparison of outcomes

real and https://www.gov.uk/discrimination-your-rights.	with and without treatment is inevitably challenging • Despite the clinical trials for MPS IVa involving more than half of the population, and there being 7 or 8 different trials assessing different aspects of the treatment and the population, and the MAA involving over 90% of the patient population, there is still criticism of the data collected, which show a lack of appreciation of the challenges involved in appraising complex, ultra-rare conditions • MPS IVa is a complex condition and the treatment is not a cure. Without measuring results for 20-30 years, it is incredibly difficult to answer questions about long term benefits without making some sensible assumptions and qualifying data analysis with the real-life experiences of patients. If we were to wait for the data, this would deny an entire generation of patients access to a treatment which is proven to deliver significant benefits. This is immoral and shows a complete lack of appreciation of the complexities involved, and how these are significantly amplified in the appraisal of complex, ultra-rare conditions • MPS IVa is an extremely complex condition and cannot be over-simplified. Given the inherent challenges with data collection and an economic model that truly reflects the benefits that the treatment brings, the weighting placed on patient feedback and qualitative data collection (such as the quality of life data collected through the MAA and patient feedback) need to be substantially increased. Yet the appraisal methods do little more than play a nod to it. The combination of these factors means MPS IVa patients are being put at a structural disadvantage because these factors are not fully accounted for within the processes used by NICE to appraise the therapy. This structural discrimination applies to any complex ultra-rare condition.

Other issues	
13. Are there any other issues that you would like the committee to consider?	I am unclear why the Committee is placing so much focus on clinical trial data. This was fully reviewed 6 years ago in the initial NICE appraisal. At that point, the treatment was approved for 5 years and The Managed Access Scheme was set up to collect additional data to respond to outstanding questions relating to the stabilisation of the disease over a longer time frame. This is absolutely where the attention of the Committee should be focused.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition?	a. The assessment parameters used in the clinical trial are appropriate to assess the severity of the condition but provide a very narrow lens on a very complex disease. This is primarily due to the challenges in finding indicators that can be objectively measured. However the vast range of qualitative data from patients, and data collected through the MAA are essential pieces of the jigsaw that paint a rich picture of the day to day impacts of the condition and the substantial benefits of the treatment. If the assessment tools and the economic model are used in isolation of these broader factors, the full picture cannot be seen and the benefits of the treatment will be grossly under-estimated.

14b. Are there any benefits of this treatment that have not been captured? 14c. What are the benefits of this treatment for carers?	b. The evidence I have given with regard to the benefits to Sam, show a broad range of benefits that have not been captured within the written papers. These benefits are also very clearly reflected in the MAA data and qualitative feedback collected by the MPS Society. c. Elosulfase Alfa substantially improves Sam's quality of life and his independence. This means that he has the energy, strength and ability to largely care for himself. For me and my husband as carers, this affords us much greater independence, it gives us the ability to work and earn a living and creates substantial, positive mental health impacts. We do not need to claim carers allowance. We do not need to claim employment benefits ourselves because we are able to work and fully support our family. We are able to provide value back into society and into the economy, as Sam will do too once he finishes full time education, assuming his access to Elosulfase Alfa continues.
15. Are there any important issues that have been missed in ERG report?	1. It is unclear why the ERG Report is putting so much focus on the clinical trial given this took place up to a decade ago. The purpose of this review is specifically to address questions regarding the longer-term stability of the disease, which was the reason for setting up the Managed Access Scheme and collecting data in the first place. The ERG Report therefore seems to have somewhat missed the point of this appraisal. 2. The Technical Engagement Papers, and the ERG Report do not focus sufficiently on the broader Quality of Life benefits reported by patients through the MAA data and associated qualitative feedback. From the perspective of the economic model, this is primarily due to the challenge of finding quality of life indicators that are measurable within the confines of the economic model. However this perfectly highlights the real problem with the appraisal – that the broader benefits to the MPSIVa population, which are exceedingly visible and apparent within the MAA data and associated qualitative feedback – are not, on paper at least, properly taken into consideration.
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement:	

- Elosulfase Alfa provides substantial physical, quality of life and well-being benefits to Sam. Over the decade of receiving treatment, Sam's health has been good (requiring very few acute medical interventions), his mobility has not deteriorated (which is remarkable given MPSIVa is a progressive disease), and his independence has increased substantially.
- Elosulfase Alfa has already changed the course of the disease for Sam, and has re-written his future, assuming he continues to receive it. It gives Sam (and us as carers) the ability to give value back into society and to the economy
- If Elosulfase-Alfa were taken away from Sam, he would be condemned to a loss in mobility and independence, and this would have devastating impacts on his mental health, his future, and our ability to function as a family. This is beyond our comprehension and would not be something we would accept.
- Substantial, broad quality of life benefits have been consistently reported by patients such as Sam, and this is also strongly reflected in the data collected through the Managed Access Scheme. The focus given to this, and the weighting applied to it through the decision making process must increase substantially if the true benefits to patients are to be properly taken into consideration.
- All MPSIVa patients fall under the protected characteristics of disability, and this entire population is being subjected to structural discrimination as a result of the methods and approach used by NICE to assess the efficacy of treatments for ultra-rare diseases. This must be properly and fully addressed within this evaluation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2)

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Tuesday 11 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with mucopolysaccharidosis type IVa and current treatment options	
About you	
1.Your name	Alex Morrison
2. Are you (please tick all that apply):	☐ a patient with mucopolysaccharidosis type IVa? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with mucopolysaccharidosis type IVa? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Rare Disease Research Partners (MPS Commercial is a Private Limited Company Registered No 08621283. MPS Commercial trades as Rare Disease Research Partners and is a wholly owned, not for profit subsidiary of the Society for Mucopolysaccharide Diseases (the MPS Society), Registered Charity in England and Wales No 1143472).
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I head the team that has collected the patient reported outcomes (PROs) throughout the elosulfase alfa managed access agreement (MAA). The PRO measures were conducted over the telephone and so myself and the team have spoken to all those patients/caregivers involved in the MAA many times over a five year period and also conducted additional research to collect the patient, caregiver and healthcare professional experience of treatment to supplement our submission to NICE. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with mucopolysaccharidosis type IVa? If you are a carer (for someone with this condition) please share your experience of caring for them.	Not applicable

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for mucopolysaccharidosis type IVa on the NHS?	The expert clinical centres in England provide excellent care for patients with MPS IVA. Elosulfase alfa is currently the only disease modifying treatment available to these patients. Before its introduction, only management of symptoms was available through supportive care and surgeries. Elosulfase alfa is the first treatment that offers the hope of slowing or halting disease in this progressive and debilitating condition. 'Current treatment' has been elosulfase alfa for most patients during the last 5 years, accessed via the Managed Access Agreement (MAA). As of February 2020, 73% (72/99) of MPS IVA patients in England had received treatment with elosulfase alfa under the MAA. In addition, a significant proportion of patients had also taken part in the clinical trials and so 26 patients had been on treatment with elosulfase alfa for between three and six years prior to joining the MAA. Patients on elosulfase alfa have reported improvements in their quality of life, particularly in regards to their energy levels which supports their ability to work, study and socialise. An extensive report on patients experience of treatment was included in the Rare Disease Research Partners evidence submission.
7b. How do your views on these current treatments compare to those of other people that you may be aware of?	As part of the Rare Disease Research Partners evidence submission preparation, we worked with our MPS Society colleagues to hold a clinician and specialist nurse meeting to discuss the changes in patients seen in the expert centre clinics and to compare them with the changes reported to us by patients. Our medical colleagues confirmed what patients were telling us and reported that patients had more energy and resilience, were more independent, slept better and had less respiratory infections. These improvements had led clinicians to view MPS IVA differently in terms of these patients now having a future, having discussions

	about university and work and undertaking surgeries that may not have been considered before when MPS IVA patients were less 'well' and able to recover and benefit from surgery.
8. If there are disadvantages for patients of **current NHS treatments** for mucopolysaccharidosis type IVa (for example how elosulfase alfa is given or taken, side effects of treatment etc) please describe these	Disadvantages of elosulfase alfa are covered in Q10. The disadvantages of supportive care are that it does not affect the progression of disease.
Advantages of this treatment	
9a. If there are advantages of elosulfase alfa over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	Patients, caregivers, clinicians and nurses have reported numerous advantages that treatment has provided and these were reported in full in our submission, please refer to the following documents: • Rare Disease Research Partners. Patient and caregiver experience of treatment with elosulfase alfa under the Managed Access Agreement. Unpublished report. March 2020 • Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. April 2020 • Rare Disease Research Partners and MPS Society. Observations of elosulfase alfa treatment benefits in specialist Lysosomal Storage Disorder centres in England. Unpublished report. January 2020.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	Elosulfase alfa has given hope to patients, to manage their disease effectively and help them achieve their full potential and lead productive and independent lives.
9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment	Yes. Patients feel better on treatment, their quality of life improves, and they feel that elosulfase alfa stabilises their disease.

that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of elosulfase over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Reported disadvantages are mainly related to the delivery method, weekly IV infusion, in terms of scheduling and sometimes cannulation. Also, under the rules of the MAA, patients could not miss more than three infusions a year, which made it difficult to travel or take holidays. Generally, patients that expressed any disadvantages felt that the benefits of treatment far outweighed any disadvantages.
Patient population	
11. Are there any groups of patients who might benefit more from elosulfase alfa or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Benefits were reported across the whole patient population.

Equality	
12. Are there any potential equality issues that should be taken into account when considering mucopolysaccharidosis type IVa and elosulfase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	Patients with MPS IVA are at a disadvantage in the NICE process. The rarity of this condition means that these minority groups of patients may be denied any new potential disease modifying treatments due to cost and evaluation processes that have difficulty dealing with small data sets.

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition?	In rare, complex, multisystemic diseases such as MPS IVA, it is difficult to capture the full impact of disease and no disease specific measures exist. Outcome measures chosen for the clinical trials represent the best available tools at the time. Assessment measures for the MAA were based on those used in the clinical trials and additional patient reported outcomes were included to capture some of the wider impacts of disease and treatment. The MAA was specifically designed to address uncertainties from the first HST with input and agreement from NICE, NHS England, BioMarin, expert clinicians and the MPS

	Society. It was therefore considered to include measures suitable for NICE to be able to make their final decision. NICE have been involved in 6 monthly patient review meetings throughout the MAA and are fully aware of how patients have responded to treatment and the fact that most patients have continued to meet the criteria for continued treatment. Again these criteria were agreed by all stakeholders as a measure of treatment response and level of benefit considered 'enough' to justify continued treatment. **Data from the MAA have proven conclusively that patients derive sufficient benefit from treatment as defined by NICE, NHS England and the other stakeholders.**
14b. Are there any benefits of this treatment that have not been captured?	Yes, the clinical trials and MAA do not capture some of the benefits that patients report. For this reason we have systematically collected additional data throughout the MAA which aim to capture the fuller treatment experience of patients. Please refer to our reports: • Rare Disease Research Partners. Patient and caregiver experience of treatment with elosulfase alfa under the Managed Access Agreement. Unpublished report. March 2020 • Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. April 2020 • Rare Disease Research Partners and MPS Society. Observations of elosulfase alfa treatment benefits in specialist Lysosomal Storage Disorder centres in England. Unpublished report. January 2020.
14c. What are the benefits of this treatment for carers?	Treatment has meant that adults and children are much more able to become independent. Many of the adult patients lead independent lives and children on treatment are able to take part in out of school activities and meet friends independently outside of the home. They are working, volunteering, attending college, going to university and thriving at school. Inevitably patients may require some help for aspects of their disease such as short stature, but many manage these well with suitable adjustments in the home and equipment such as steps, lever taps and adapted toilets and vehicles.

While some parents work part time to accommodate home infusions, others are more able to work as children are better able to cope with a full school day and need less time off due to illness. Many children receive their infusions at school to minimize any impact on their education.

Please refer to our survey report for many first-hand accounts of how treatment has affected patients and carers employment, education and leisure time. Here are just two examples:

"Before treatment I could not complete more than an hour or two at school for being in constant pain and discomfort with no energy to get through the day, whereas now I drive myself to college, complete a full day and then drive myself to work four a 6 to 8 hour shift 4 days a week, all without any walking aids or assistance, no wheelchair and very little pain relief. In school I had a 1 to 1 assistant which I no longer need."

"[Before treatment] I found myself having to turn down work related lunches and outings, as locations could sometimes be a bit too far for me to walk from the office building. I was increasingly unable to lift small loads, and became short of breath whilst walking small stretches, such as carrying a laptop to a meeting room. These were milestones I had reached whilst on the enzyme replacement therapy trial, but after a short break, I found myself held back from reaching them. Having been on Vimizim for the past 5 years, I have noticed the effect that having more endurance has had on my professional life. I am able to socialise a lot more at work than I did in the beginning, I have worked extra overtime as I don't find myself exhausted by the end of the day. All these factors have led to me seeing multiple promotions and nominations for industry awards."

15. Are there any important issues that have been missed in ERG report?	It is important to recognise the effort and commitment that patients and their families have given to ensuring a thorough and robust data collection was possible during the MAA. They have followed the strict restrictions of the MAA that has made taking holidays difficult and attended their clinics for tests and completed numerous patient reported outcome questionnaires, all in the knowledge that treatment could be removed at any time if they did not 'pass' the next assessment. The emotional impact of this process should not be underestimated. Patients lived through the initial HST, the initial decision not to recommend elosulfase alfa and the year long wait to establish the MAA during which time ex-clinical trial patients had their treatment withdrawn for over a month (1). Patients have entered the MAA in good faith and for all those involved including the clinicians and the MPS Society it has successfully shown what it was designed to show, i.e. that patients have continued benefit on treatment. The fact that the whole HST process is being repeated raises genuine fear and anxiety in all concerned that this transformative treatment may be rejected again. With a large proportion of UK patients having taken part in the clinical trials and most eligible patients now being treated under the MAA, elosulfase alfa has been a mainstay of treatment for MPS IVA for the past decade. The full impacts of a return to supportive care only should be carefully considered when considering the cost effectiveness of treatment and the practicality of removing such an established treatment. The NICE team involved in the MAA should be fully involved in this HST and their comments should also be sought if they have not been already. 1. Roberts C, Lavery C, Nicholls N, Jain M, Hendriksz C, Upadhyaya S, Jessop E. Multi-stakeholder engagement leading to access to treatment for MPS IVA (Morquio A) – a model for the ultra-rare disease community. Poster session presented at: 14th International Symposium on Mucopolysaccharidoses (MPS) and Related Disease; 2016 Jul14-17; Bonn. Available at: https://rd-rp.com/wp-content/uploads/2019/12/Poster-118_print_A4.pdf

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- The MAA has confirmed the long-term benefits of elosulfase alfa as defined by NICE and the other stakeholders.
- With treatment, patients are able to live independent, productive lives.
- With treatment patients' quality of life is vastly improved.
- Treatment reduces the need for carer support.
- Patients of all ages have reported significant sustained benefits.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2)

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Tuesday 11 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with mucopolysaccharidosis type IVa and current treatment options	
About you	
1.Your name	**Sophie Thomas**
2. Are you (please tick all that apply):	☐ a patient with mucopolysaccharidosis type IVa? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with mucopolysaccharidosis type IVa? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	The MPS Society
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I am a patient advocate and have carried out interviews and surveys to gather evidence for this re-evaluation ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with mucopolysaccharidosis type IVa? If you are a carer (for someone with this condition) please share your experience of caring for them.	Please see patient carer organisation submission (29.03.2021)
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for mucopolysaccharidosis type IVa on the NHS?	Please see patient carer organisation submission (29.03.2021)

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for mucopolysaccharidosis type IVa (for example how elosulfase alfa is given or taken, side effects of treatment etc) please describe these	Please see patient carer organisation submission (29.03.2021)
Advantages of this treatment	
9a. If there are advantages of elosulfase alfa over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment	Please see patient carer organisation submission (29.03.2021)

that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of elosulfase over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Please see patient carer organisation submission (29.03.2021)
Patient population	
11. Are there any groups of patients who might benefit more from elosulfase alfa or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Please see patient carer organisation submission (29.03.2021)

Equality	
12. Are there any potential equality issues that should be taken into account when considering mucopolysaccharidosis type IVa and elosulfase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition?	14a.There are no specific validated assessment tools for assessing severity of MPS conditions in clinical trials. The multi systemic nature of the condition means it is also difficult to identify meaningful endpoints. We are therefore, always faced with uncertainties that are difficult to quantify. This was the purpose of the MAA, to appropriately assess and monitor the impact of the condition and the effects of the treatment on patients. The MAA criteria and assessments differed from those captured in the clinical trial to try and address not just the clinical uncertainties raised in the first HST evaluation but to qualify and verify the

14b. Are there any benefits of this treatment that have not been captured? 14c. What are the benefits of this treatment for carers?	impact on patients and carers by capturing real world evidence and specific quality of life measures. Maybe the question should be 'are the assessment tools used in the MAA, appropriate for assessing the severity of this condition?' 14b. There were areas of benefit not captured through the MAA and these have been captured and reported by both the patient organisation and RDRP and have been submitted as evidence for this re-evaluation. Please see; patient carer organisation submission and attachments, outlined below. 14c. Please see; patient carer organisation submission and attachments, outlined below. (1) Rare Disease Research Partners and MPS Society. Observations of elosulfase alfa treatment benefits in specialist lysosomal storage disorder centres in England. Unpublished report. January 2020 (2) Rare Disease Research Partners. Patient and caregiver experience of treatment with elosulfase alfa under the managed access agreement. Unpublished report. March 2020. (3) Rare Disease Research Partners and MPS Society. MPS IVA patient and caregiver experience of treatment – UK survey. Unpublished report. April 2020. (4) Thomas S MA. The educational journey of individuals with MPS IVA Morquio disease. International MPS Symposium; Bonn Germany. Poster presentation 2016. (5) [redacted]
15. Are there any important issues that have been missed in ERG report?	It is concerning that, the focus of the ERG's critic, has been largely weighted to the clinical trial data and not the data collected and reviewed as part of the 5 year MAA. It is also concerning that the evaluation and outcomes of this ERG review are not balanced against the review conducted in 2015, where the challenges in interpreting clinical research for rare diseases was recognised.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Well tolerated and wanted. Compliance has been exceptional for this group of patients

- Treatment benefits have been seen in all ages of patients
- Outcomes have benefitted patients and carers greatly
- Patients are contributing to Society more
- Surgeries are being considered that were not previously thought viable

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

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☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2)

Thank you for agreeing to comment on the ERG report for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 1 October 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with mucopolysaccharidosis type IVa and current treatment options	
About you	
1. Your name	**James Davison**
2. Name of organisation	**Great Ormond Street Hospital**
3. Job title or position	**Consultant Paediatric Metabolic Medicine**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	In children with MPS IVa, a successful treatment would improve growth, slow decline in respiratory function, improve endurance and ability to maintain independent mobility. Long term a successful treatment would improve life expectancy.
9. What do you consider a clinically significant treatment response? (For example, a	

reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is very substantial unmet need for patients with MPS IVa. Without disease-modifying treatment this is a severe life-limiting disorder.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Patients are treated by a specialist centre as part of the lysosomal storage disease Highly Specialised Service. (LSD HSS). Multiple professionals are required as part of the treatment team. - metabolic - respiratory -cardiology - orthopaedics - neurosurgery - ENT - anaesthetics - OT - physio - dental -ophthalmology Disease-modifying treatment with elosulfase alfa is offered via the existing MAA.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Refer to guidelines cited by Dr E Murphy in her previous submission
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined, with referral to LSD HSS centre.
• What impact would the technology have on the current pathway of care?	The technology already forms part of the current pathway of care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	IT is already in use in NHS clinical practice.
• How does healthcare resource use differ between the technology and current care?	N/A
• In what clinical setting should the technology be used? (For example,	LSD HSS specialist clinic, but delivered in home setting where appropriate.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	N/A - investment to continue current use of technology
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Compared to historic "SoC" the technology has demonstrated clinically meaningful benefits already.
• Do you expect the technology to increase length of life more than current care?	It is anticipated that the early benefits seen in clinical trials and also evidenced in the MAA would translate to a survival benefit in the long term
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. This is evidenced by the outcomes seen in clinical trials, the MAA, and reported by patients and families in clinical experience.
14. Are there any groups of people for whom the technology would be more or less effective	There are some very mild "attenuated" patients (e.g. have just issues with hip dysplasia) who may derive less benefit. Others with very advanced disease may not derive as greater benefit. Very early initiation is anticipated to result in improved longer term outcome

(or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is current care, and has been demonstrated to be well tolerated and integrated into SoC.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with other Enzyme Replacement Therapies treatment would be stopped in line with guidelines, including where no benefit is derived, or there are unsurmountable problems such as unmanageable infusion associated reactions.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The models used have incorporated broad range of health-related benefits. Use of ERT coincides with advances in other surgical practices which together result in further benefit to patients.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This is the first (and currently only) disease modifying treatment for MPS IVa.
• Is the technology a 'step-change' in the management of the condition?	As above. It is not "curative" but significant benefit is noted in clinical practice.
• Does the use of the technology address any particular unmet need of the patient population?	It aims to be a disease-modifying treatment by treating the specific biochemical defect.
19. How do any side effects or adverse effects of the technology	The main side effects are infusion associated reactions, which require management if they occur as for other enzyme replacement therapies.

affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Trials included UK population and reflected current clinical practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	6MWT as measure of endurance, and measures of respiratory function.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but	

have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No (other than patient-reported benefits noted in clinical encounters)
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE highly specialised technology guidance [HST2]?	No
23. How do data on real-world experience compare with the trial data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	

24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Lack of robust comparative data for ESA compared to standard of care and the heterogeneity of mucopolysaccharidosis type IVA	MPS IVa is “heterogenous” but for all patients included is very severe – they are “heterogeneous” within the severe end of the disease spectrum. My major concern is the desire to have a homogenous cohort restricts the numbers being included and weakens the ability of the analysis to generate reliable conclusions. The vast majority of patients are now receiving ESA and so the use of the historic comparator cohorts is the best available evidence.
Key issue 2: Use of ESA treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation	This applied to those patients in the early phase clinical trials who may have received placebo or lower dosing initially. However, later trials and all patients within the NHSE MAA have had the recommended dose. Those patients who may have had “suboptimal” dosing for a period of time in the trials will have moved to standard dosing; if the modelling assumes they have had 2mg/kg/QW throughout this may lead to an underestimate of the treatment effect.

in some of the ex-trial 'managed access agreement' patients	
Key issue 3: Absence of a systematic literature review to identify studies for standard of care	
Key issue 4: Clinical heterogeneity in the clinical analyses and inappropriate methods for handling of missing data	I disagree that there are such profound differences between the patients included. All have severe MPS IVa. There is heterogeneity in the stage of disease that their disease may have reached at different timepoints – which will depend on age, and age treatment commenced.
Key issue 5: Use of inconsistent timepoints within and between studies for assessment of clinical outcome data	
Key issue 6: Clinical data used in the model: The data included in the economic model are unfit for decision making.	

Key issue 7: Modelling approach: The use of a wheelchair-based model is unlikely to capture the impact of ESA on patients' disease and the thresholds for change in wheelchair use in the model are contradictory to the underlying clinical data.	Wheelchair-based model does reflect important real-world progression of the disease, and there are correlations demonstrated with other parameters from lung function and 6MWT.
Key issue 8: Estimation of wheelchair dependency in the model: Given the availability of annual wheelchair use data, it is unclear to the ERG why these were not used by the company. The ERG disagrees with the company's assumptions of constant decline in the standard of care arm and the company's assumption that after year 1 in the model, only 0.01% of ESA patients progress to the next	

(more dependent) wheelchair state in the model.	
Key issue 9: Mortality - The company's approach to estimating mortality is overestimating survival in the model.	
Key issue 10: Estimation of quality of life in the model: The company's justification for having treatment-specific utility values by wheelchair category is inconsistent with the company's justification for having a wheelchair-based model and it double counts the benefits associated with ESA.	
Key issue 11: ESA costs - The company underestimated the treatment costs in the analysis.	

Are there any important issues that have been missed in ERG report?	My over-arching concern about the approach taken by ERG is that there is a drive to only using very short-term outcome data, i.e. 1 or 2 years of treatment, and then extrapolating to the (very) long term benefit. Some patients have been receiving ESA for upto ~ 10 years and yet long term data is not considered. Despite the rationale given for wanting to limit analaysis to the short term data, the assumption that most benefit is only seen form ESA in the first 1-2 years does not represent what is seen in clinical practice, where we observe continual accrual of benefit.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- In clinical practice we see meaningful benefit to patients from long-term ESA treatment
- Treatment started at earlier age is observed in practice to result in greater benefit
- The concerns about “heterogeneity” in the cohort are important but overstated, with all patients included having “severe” MPS IVa.
- Compared to other similar rare diseases the already-extant evidence base from the extensive clinical trials of ESA for MPS IVa have demonstrated clear signal for benefit from treatment, necessarily based on relatively short-term outcomes in the context of a life-long disorder where benefit would be expected to still be seen 30 years later.
- The analysis seems to be “missing a trick” by not grappling with the available longer term outcome data.

Thank you for your time.

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Clinical expert statement & technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2)

Thank you for agreeing to comment on the ERG report for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Tuesday 11 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with mucopolysaccharidosis type IVa and current treatment options	
About you	
1. Your name	**Elaine Murphy**
2. Name of organisation	**University College London Hospitals NHS Foundation Trust**
3. Job title or position	**Consultant adult inherited metabolic disease**
4. Are you (please tick all that apply):	☐ **X** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **X** other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow progression of disability related to MPS IVA.
9. What do you consider a clinically significant treatment response? (For example, a	Improvement or slowing of decline in mobility. Reduced dependence on mobility aids (eg reduced wheelchair use). Reduced need for analgesia. Stable or improved respiratory function. Improved quality of life and activities of daily living of patients (patient reported outcomes) with reduced caregiver assistance required.

reduction in disease activity by a certain amount.)	Increased life expectancy. Meeting the criteria defined by the MAA (stable or improved): Endurance - 6MWT Pulmonary function – FEV1 and FVC
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Supportive multidisciplinary measures (physiotherapy, occupational therapy) Pain management Joint surgery (including replacement) Ventilatory and airway support (non-invasive ventilation) Cervical spinal cord surveillance (with / without surgery) Cardiac surveillance (with / without medical management or surgery) Hearing surveillance (with / without medical management or surgery) Opthalmology surveillance (with / without medical management or surgery) This review is of the MAA for Elosulfase alfa – so the majority of patients with MPS IVA are already receiving treatment.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Recommendations for the management of **MPS** IVA: systematic evidence- and consensus-based guidance. Akyol MU, Alden TD, Amartino H, Ashworth J, Belani K, Berger KI, Borgo A, Braunlin E, Eto Y, Gold JI, Jester A, Jones SA, Karsli C, Mackenzie W, Marinho DR, McFadyen A, McGill J, Mitchell JJ, Muenzer J, Okuyama T, Orchard PJ, Stevens B, Thomas S, Walker R, Wynn R, Giugliani R, Harmatz P, Hendriksz C, Scarpa M; MPS Consensus Programme Steering Committee; MPS Consensus Programme Co-Chairs.Orphanet J Rare Dis. 2019 Jun 13;14(1):137. doi: 10.1186/s13023-019-1074-9. International guidelines for the management and treatment of Morquio A syndrome. Hendriksz CJ, Berger KI, Giugliani R, Harmatz P, Kampmann C, Mackenzie WG, Raiman J, Villarreal MS, Savarirayan R.Am J Med Genet A. 2015 Jan;167A(1):11-25. doi: 10.1002/ajmg.a.36833. In addition the NHSE MAA mandated clinical and biochemical parameters that were collected in all patients.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Broadly speaking the pathway of care is well defined (with the specialist paediatric and adult LSD centres). Given the rarity of the condition, and the heterogeneity of phenotypes (from mild to severe) minor differences in type or timing of interventions may occur.
• What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used in a similar way to the current MAA. In clinical practice – some monitoring is likely to change eg. increased interval between echocardiograms in stable patients; reduced frequency of measurement of urine GAGs.

• How does healthcare resource use differ between the technology and current care?	The technology will be used in a similar way to the current MAA.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescribed and monitored by specialist LSD services.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	N/A. The majority of diagnosed patients are already receiving treatment. As more patients are diagnosed and start on treatment additional resources (homecare nursing etc) might be required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes (compared with natural history prior to treatment with Elosulfase alfa)
• Do you expect the technology to increase length of life more than current care?	Given that > 60% of deaths in this condition are reported to be related to respiratory issues, and that ESA in the MMA was shown to stabilise or improve pulmonary function then an increase in life expectancy might be expected.
• Do you expect the technology to increase	Yes.

health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There may be a small number of patients with extremely mild disease for whom elosulfase alfa would have little perceived benefit – this is not known as data has not been reported separately for this group. There is likely to be some patients with a very severe, or end-stage phenotype, or with another concomitant condition for whom elosulfase alfa would not be appropriate or of significant clinical benefit.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The majority of diagnosed patients are already receiving treatment. Intravenous ERT is a well-established and generally well-tolerated treatment.
16. Will any rules (informal or formal) be used to start or stop	Although not yet formally agreed – it is likely that start / stop criteria will be suggested by the LSD centres.

treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	

• Is the technology a 'step-change' in the management of the condition?	Yes – if compared to baseline when patients did not have access to Elosulfase alfa.
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Limited adverse effects – occasional infusion related reactions in some patients. Inconvenience of a regular intravenous infusion. No specific safety concerns.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Broadly speaking – although increased awareness since the availability of treatment is likely to have been associated with more monitoring, access to supportive care and possibly earlier interventions for some patients (both papers with suggested guidelines for management of MPS IVA (Aykol et al, OJRD 2019 and Hendriksz et al, Am J Med Genet 2015) were published after the first of the clinical trials of ESA were published and may have influenced practice).

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall improvements in endurance. Patients' ability to complete activities of daily living with reduced fatigue and need for rest or mobility aids.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No.

of NICE highly specialised technology guidance [HST2]?	
23. How do data on real-world experience compare with the trial data?	The patient narrative is of increased energy and functional ability on treatment with ESA. This is likely to be multifactorial in nature and so difficult to capture with individual surrogate markers. The MAA real world experience is now published (Clear et al. OJRD 2021).
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Lack of robust comparative data for ESA compared to standard of care and the heterogeneity of mucopolysaccharidosis type IVA	It is worth noting that the natural history study (reported in Harmatz et al, Mol Genet Metab 2015) included patients from 3 UK sites (who subsequently participated in the MAA) – and so this group would have been reasonably comparable to ESA treated patients.
Key issue 2: Use of ESA treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation	

in some of the ex-trial 'managed access agreement' patients	
Key issue 3: Absence of a systematic literature review to identify studies for standard of care	
Key issue 4: Clinical heterogeneity in the clinical analyses and inappropriate methods for handling of missing data	
Key issue 5: Use of inconsistent timepoints within and between studies for assessment of clinical outcome data	
Key issue 6: Clinical data used in the model: The data included in the economic model are unfit for decision making.	

Key issue 7: Modelling approach: The use of a wheelchair-based model is unlikely to capture the impact of ESA on patients' disease and the thresholds for change in wheelchair use in the model are contradictory to the underlying clinical data.	
Key issue 8: Estimation of wheelchair dependency in the model: Given the availability of annual wheelchair use data, it is unclear to the ERG why these were not used by the company. The ERG disagrees with the company's assumptions of constant decline in the standard of care arm and the company's assumption that after year 1 in the model, only 0.01% of ESA patients progress to the next	

(more dependent) wheelchair state in the model.	
Key issue 9: Mortality - The company's approach to estimating mortality is overestimating survival in the model.	
Key issue 10: Estimation of quality of life in the model: The company's justification for having treatment-specific utility values by wheelchair category is inconsistent with the company's justification for having a wheelchair-based model and it double counts the benefits associated with ESA.	
Key issue 11: ESA costs - The company underestimated the treatment costs in the analysis.	

Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the evaluation committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the evaluation committee meeting.

Deadline for comments **5pm on Tuesday 11 May 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**The MPS Society (also representing the views of RDRP our wholly owned subsidiary)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Lack of robust comparative data for elosulfase alfa compared to standard of care and the heterogeneity of mucopolysaccharidosis type IVA	No	Given that the ERG are unable to state even the *direction* of impact this will have on the results is it possible this issue is a non-issue. NICE consistently use ERG's who have little or no experience in evaluating diseases that affect tiny populations. This really should not be raised as an issue for HST assessment as it fundamentally represents structural discrimination against people affected by rare diseases. This statement contradicts the ERG's view in 2015 where it is recorded on the NICE website that '***The ERG considered that, although there were some methodological shortcomings, the systematic review captured all relevant evidence including several reasonable quality clinical studies. It noted some challenges in interpreting the clinical trial data (which are not uncommon in clinical research for rare diseases)'*** Included also was the list of areas the ERG were referring to This treatment group represents the largest cohort of patients enrolled on a clinical trial (7 clinical studies with 255 patients enrolled), with 75 English patients latterly enrolled on a MAA, which has been in place for the past 5 years with some patients being on active treatment for over 10 years, this is the standard of care for this patient group.

Key issue 2: Use of elosulfase alfa treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation in some of the ex-trial 'managed access agreement' patients	**No**	It is our understanding that this was part of one of the early dose ranging clinical trial studies. All pts enrolled on the MAA for last 5 years have been on the authorised dose of 2.0mg/kg/QW. If this is in fact true, why is the ERG raising this historical point as an issue? If this is not the case we would agree that the preferable dose is 2.0 mg/kg/QW however this should not mean excluding this data, especially given the complaint in 'Key Issue 1' was regarding lack of data. Again does the ERG have the skills and experience to evaluate evidence for diseases affecting tiny populations. Given that the ERG are unable to state the ***direction*** of impact this will have on the results is it possible this issue is a non-issue.
Key issue 3: Absence of a systematic literature review to identify studies for standard of care	**Y**es	Lack of a systematic literature review could be a legitimate complaint. However there are only 637 articles that include information on MPS IV in pubmed (search performed 5th May 2021). A search performed to retrieve articles on the Standard of Care in MPS IV returned 3 articles none of which described the standard of care in the UK. Is this really a genuine concern or does this again reflect the ERG's lack of understanding of evidence as it relates to small populations. 10 mins on pubmed will confirm this is an area with very little published data and the ERG are unable to state the ***direction*** of impact this will have on the results this issue is a non-issue. It is not clear what the ERG think has been missed.
Key issue 4: Clinical heterogeneity in the clinical analyses and inappropriate methods for handling of missing data	**N**o	Given the complaint in 'Key Issue 1' regarding lack of data it shows a lack of understanding of small populations to complain about some of the data. Is the missing data related to clinical trial data, MAA data or both? MAA data has been routinely and systematically collected by all the Highly Specialised clinical services. The MAA criteria was based on the uncertainties raised by the committee

		in the first HST evaluation. This data has been presented and reviewed on a 6 monthly basis by both NICE and NHSE. The ERG are again unable to state the *direction* of impact this will have on the results.
Key issue 5: Use of inconsistent timepoints within and between studies for assessment of clinical outcome data	No	The ERG's focus should have been on the clinical outcome data collected through the MAA. The clinical trial data has already been subject to an ERG review with uncertainties raised and data collected to address these. It is concerning that the ERG appear to have either not understood the scope of the re-evaluation or that their brief was not clear.
Key issue 6: Clinical data used in the model: The data included in the economic model are unfit for decision making.	No	The ERG's lack of skill in the interpretation and analysis of data from tiny populations is again evident not only are they unable to state the *direction* of impact this will have on the results, but also their proposed solution appears to be hyper-focused on only one piece of the available data. This was not the case when the ERG evaluated the data in 2015.
Key issue 7: Modelling approach: The use of a wheelchair-based model is unlikely to capture the impact of elosulfase alfa on patients' disease and the thresholds for change in wheelchair use in the model are contradictory to the underlying clinical data.	No	It is not clear if the ERG's assertion in this issue '**there is evidence to support a strong correlation between endurance and mobility measures (6MWT) and patients' respiratory measures (FVC) with patient's EQ-5D-5L/HRQoL'** is based on MPS IV data. If it is then this is a valid issue. If it is not then this represents a failure to understand the disease. It is unclear (given the stated strong correlation) why the ERG are not able to predict the direction of impact of this issue.
Key issue 8: Estimation of wheelchair dependency in the model: Given the availability of	No	Why when the ERG state in issue 7 '**there is evidence to support a strong correlation between endurance and mobility measures (6MWT) and patients' respiratory measures (FVC) with patient's EQ-5D-5L/HRQoL**' can they then say

annual wheelchair use data, it is unclear to the ERG why these were not used by the company. The ERG disagrees with the company's assumptions of constant decline in the standard of care arm and the company's assumption that after year 1 in the model, only 0.01% of elosulfase alfa patients progress to the next (more dependent) wheelchair state in the model.		in this issue '**The ERG has several concerns around the estimates used to derive the increase in WC dependency for SoC patients in the following years of the model, through the use of 6MWT and FVC outcomes.'** If the ERG are so sure that this is wrong and '**biased'** how are they not able to estimate an impact on cost-effectiveness?
Key issue 9: Mortality - The company's approach to estimating mortality is overestimating survival in the model.	**N**o	This is a reasonable concern.
Key issue 10: Estimation of quality of life in the model: The company's justification for having treatment-specific utility values by wheelchair category is inconsistent with the company's justification for having a wheelchair-based model and it double counts the benefits associated with elosulfase alfa.	**n**o	The ERG assertion that WC states have the same utility in each arm seems clinically reasonable. But why are the ERG not able to say what impact this would have on cost-effectiveness?
Key issue 11: Elosulfase alfa costs - The company underestimated the treatment costs in the analysis.	**N**o	Are the ERG saying that patients will weigh more. If so while cost is related to dose and dose is weight determined this is a legitimate issue.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Deviation From Stakeholder Agreement	All	**No**	It is concerning that NICE do not appear to have a clear process for the re-evaluation of technologies at the end of a HST MAA. This is supposed to be a review of the MAA and not a full clinical trial review. It is concerning that the ERG either does not understand the process, the context, or, has not been given a clear enough brief.
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Multi-stakeholder engagement leading to access to treatment for MPS IVA (Morquio A) – a model for the ultra-rare disease community(BM)

Charlotte Roberts,[1] Christine Lavery,[1] Nigel Nicholls,[2] Mohit Jain,[2] Christian J Hendriksz,[3] Sheela Upadhyaya,[4] Edmund Jessop.[5]

[1]The Society for Mucopolysaccharide Diseases (MPS Society), Buckinghamshire, UK; [2]BioMarin Europe Ltd, London, UK; [3]Salford Royal NHS Foundation Trust, Salford, UK; [4]National Institute for Health Care Excellence (NICE), London, UK; [5]National Health Service (NHS) England, UK.

Objectives

To achieve reimbursement for elosulfase alfa for MPS IVA patients resident in England.

Background

- MPS IVA is an ultra-rare disease affecting less than 100 patients in England.
- In 2013, responsibility for the reimbursement decision making process for treatments for rare diseases, formerly governed by the Advisory Group for National Specialised Services, was replaced by a joint process involving the Highly Specialised Technologies Evaluation Committee of NICE and the Programme of Care Group of NHS England.
- The only treatment currently available, elosulfase alfa, was licensed by the European Medicines Agency on 28th April 2014.
- The UK had been a major contributor to the Phase III clinical trial with 35 patients being enrolled out of the 176 recruited worldwide.
- Interim funding was not available when elosulfase alfa was licensed and there was a high degree of interest and concern in continuing access to treatment in England.
- Although patients who had taken part in the clinical trial continued to receive free drug, other English MPS IVA sufferers had no access to treatment.

Methods

On the 21st November 2014, a 10 year old boy, supported by the MPS Society legally challenged NHS England's scorecard decision method. This marked the start of a year long process involving the engagement of all stakeholders to develop a workable solution for treatment access (Figure 1). Patients together with the patient organisation MPS Society UK, members of Parliament and clinicians canvassed NHS England and the Department of Health for a fair process with equal access to therapies as for common disorders (Figure 2).

This resulted in elosulfase alfa for MPS IVA being referred to NICE for full evidence review and decision. During the NICE process, the MPS Society suggested a robust procedure whereby all patients that met a set of criteria would be able to access treatment (Figure 3). Stopping criteria were also included for the first time ever. This was incorporated by NICE and announced in their draft guidance in September 2015.

The development of the Managed Access Agreement (MAA) became a working partnership between NHS England, NICE, the MPS Society, BioMarin and a clinical expert.

The MAA was designed to be inclusive for patients, ensuring response to treatment in a minimum of 4 out of 5 criteria through consistent clinical and quality of life monitoring. An intensive follow up programme and multi domain assessments would be required and treatment would stop for those not meeting treatment targets (Table 1).

Results

On 16th December 2015 NICE guidance recommended elosulfase alfa for patients in England via the MAA.[1,2] As of 31st May 2016, a total of 46 patients have been recruited to the MAA through 7 hospitals in England. This represents 48% of the 95 patients known to have MPS IVA in England. Of these, 27 patients previously took part in the clinical trials for elosulfase alfa, and 19 patients are receiving this new treatment for the first time.

Table 1. Response criteria for continued treatment[2]

Response criteria	Naïve patient (in 1st year of treatment)	Previously treated patients (2nd year or more on treatment)
Improvement of 6 MWT or 25ft Ambulation Test	10% Improvement over baseline	Remains 5% above baseline
Improvement in FVC or FEV-1	5% Improvement over baseline	Remains 2% above baseline
Stabilisation defined as no adverse change in the numerical value in two of the following three measures: • Quality of Life as measured by the EQ5D-5L or MPS HAQ Caregiver Domain • Beck depression inventory • Adolescent Paediatric Pain Tool or Brief Pain Inventory depending on age	Stabilisation	Stabilisation
Reduction in urinary keratan sulfate	20% Reduction from baseline	Remain reduced at least 20% from baseline value
Decline in ejection fraction as measured by echocardiogram	Decline of less than 10% from baseline	Decline of less than 10% from baseline

FEV: forced expiratory volume, FVC: forced vital capacity, MWT: minute walk test

Figure 3. The Managed Access Agreement criteria[2]

Start criteria
- Confirmed diagnosis of MPS IVA
- Confirmed enzymatic test, elevated urinary keratan sulfate and mutation analysis
- Sign up to the 'Managed Access Patient Agreement'
- Full set of baseline assessments obtained for patients over 5 years of age

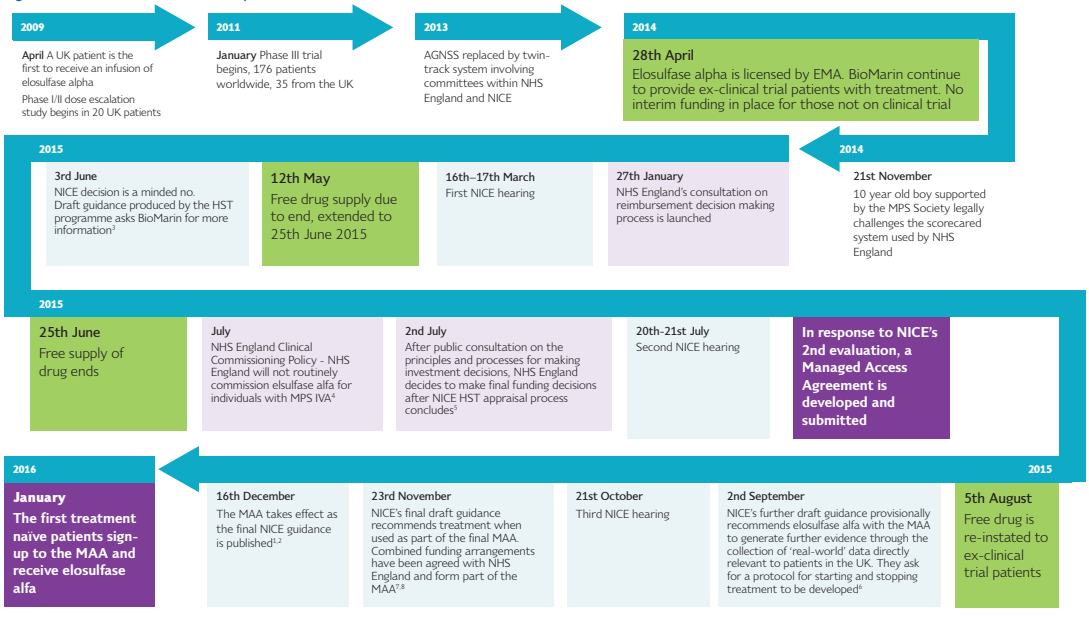
Exclusion criteria
- Patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g. cancer or multiple sclerosis
- Patient has a lung capacity (FVC) of less than 0.3 litres and requires ventilator assistance
- Patient is unwilling to comply with the associated monitoring criteria

Stop criteria
- Non-compliance with assessments for continued therapy (non-compliance is defined as fewer than three attendances for assessment in any 14 month period)
- Patient fails to meet 4 of the 5 treatment response criteria (Table 1)
- Patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved

Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures.

FVC: forced vital capacity.

Figure 1. The reimbursement decision process



AGNSS: Advisory Group for National Specialised Services; EMA: European Medicines Agency; HST: Highly Specialised Technologies

Figure 2. MPS IVA patients, families, the MPS Society and MPs, campaign for treatment access

- Engagement with 40 MPs, parliamentary questions led by Greg Mulholland, MP
- 3 meetings with the Minister for Life Sciences George Freeman
- 2 Adjournment Debates
- MPS Society hosted Westminster Hall event attended by MPs and peers, pharma representatives, patient organisations and the BBC
- 6 protests
- Parent met with the Prime Minister David Cameron
- Online petitions 'NHS England's scorecard system denies access to treatment for ultra-rare diseases' and 'Call for interim funding'
- Articles in the national and local press
- Social media campaign #fundourdrugsNOW #fight4treatment

Clockwise from left: Kamal (left) and Sam outside 10 Downing Street; Luke (left) and Olivia campaigning; Sunday Express cover story from 12 July 2015, and Kamal (left) and Sam campaigning with MPs, parents and members of MPS Society.

> "There have been a couple of signs of Vimizim doing something…I have been in the garden for the first time in a long time last week and for the first time ever, I saw the legs of a caterpillar!! This may seem daft and simple, but due to the clouding of my corneas I have never seen much detail on anything.
>
> A patient's experience of treatment

Conclusions

In an environment where health systems are having to choose between high cost drugs and the funding of other health resources, the MAA, with a confidential financial arrangement, offers all patients meeting the treatment criteria access to reimbursed therapy in the first 12 months. The MAA will be subject to annual review under the chairmanship of NICE and the data collected will be used to assess whether NICE will continue to fund the treatment after the 5 year term of the MAA.

Whilst we are in the first year of this new initiative, MPS IVA patients have embraced the MAA and recognised that adherence to the MAA is the only way forward to ensure continued access to treatment. Only time will tell if the stopping criteria are fair and if patients affected by common disorders will become subject to similar requirements in the future to ensure equity across all aspects of health.

Society for Mucopolysaccharide Diseases
www.mpssociety.org.uk

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the evaluation committee to help it make decisions at the evaluation committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the evaluation committee meeting.

Deadline for comments **5pm on Tuesday 11 May 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS England & Improvement**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NONE**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Lack of robust comparative data for elosulfase alpha compared to standard of care and the heterogeneity of mucopolysaccharidosis type IVA		
Key issue 2: Use of elosulfase alpha treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation in some of the ex-trial 'managed access agreement' patients	**No**	If NICE gives approval for the drug NHSEI will only commission at the recommended does in the EU marketing authorisation
Key issue 3: Absence of a systematic literature review to identify studies for standard of care	**No**	NHSEI would support a systematic literature review acknowledging this is a rare disease which may have a relatively limited evidence base
Key issue 4: Clinical heterogeneity in the clinical analyses and inappropriate		

methods for handling of missing data		
Key issue 5: Use of inconsistent timepoints within and between studies for assessment of clinical outcome data		
Key issue 6: Clinical data used in the model: The data included in the economic model are unfit for decision making.		
Key issue 7: Modelling approach: The use of a wheelchair-based model is unlikely to capture the impact of elosulfase alpha on patients' disease and the thresholds for change in wheelchair use in the model are contradictory to the underlying clinical data.		
Key issue 8: Estimation of wheelchair dependency in the model: Given the availability of annual wheelchair use data, it is unclear to the ERG why these were not used by the company. The ERG disagrees with the company's assumptions of constant decline in the standard of care arm and the company's assumption that after year 1 in the		

model, only 0.01% of elosulfase alpha patients progress to the next (more dependent) wheelchair state in the model.		
Key issue 9: Mortality - The company's approach to estimating mortality is overestimating survival in the model.		
Key issue 10: Estimation of quality of life in the model: The company's justification for having treatment-specific utility values by wheelchair category is inconsistent with the company's justification for having a wheelchair-based model and it double counts the benefits associated with elosulfase alpha.		
Key issue 11: Elosulfase alpha costs - The company underestimated the treatment costs in the analysis.		

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2)

ERG review of company's response to technical engagement report

September 2021

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/08/34T.

1 Introduction

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2) [ID1643]. Each of the issues outlined in the technical report are discussed in further detail in Section 3.

The company's updated base case analyses are outlined in Section 2 while the ERG's analyses are reported in Section 4.

2 Updated company base case analyses

The company's updated incremental cost-effectiveness results post TE are reported in Table 1, with the agreed patient access scheme (PAS) discount of [redacted] per 5ml vial. The company has not provided probabilistic results after TE.

Table 1. Company's deterministic base case results (discounted except for life years gained)

Interventions	Total Costs (£)	Total LYG undiscounted	Total QALYs	Incremental costs (£)	Incremental LYG undiscounted	Incremental QALYs	ICER (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Elosulfase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

3 ERG review of issues

3.1 Issue 1: Lack of robust comparative data for elosulfase alpha compared to standard of care and the heterogeneity of mucopolysaccharidosis type IVA

The Evidence Review Group (ERG) and the company are both in agreement that mucopolysaccharidosis type IVA is heterogeneous condition and so the ERG considers it important that the data used to inform standard of care (SoC) and elosulfase alfa (ESA) are from suitably matched patients to enable a meaningful clinical comparison. Unfortunately there is a lack of direct comparative study data for SoC versus ESA and so alternative methods are required to enable a comparison. The ERG is concerned that a naïve comparison between the ESA data from the managed access agreement (MAA) and SoC from the MOR-001 trial is subject to clinical heterogeneity. However, the ERG also considers the propensity score matching (PSM) results reported by the company in their clarification question response to be unreliable due to flaws in the coding and analysis of the patient level data that were discussed in detail in the ERG report.

The ERG was particularly concerned that MPS IVA comprises a heterogenous patient population and so individual patients could have markedly different baselines and treatment responses. The ERG noted that not all patients had baseline and follow-up data at each time point in the company's analyses. The company's previous approach of comparing the mean estimates of all patients observed at each time point, does not therefore account for the fact that these represent different cohorts of patients with potentially very different outcomes. Additionally, it was not possible to assess the direction of the resulting bias from the company's approach. The ERG therefore considered it important that the company instead conduct complete case analyses (CCAs), where the same cohort of patients are followed from baseline to each subsequent timepoint. As part of technical engagement (TE) the ERG recommended the company conduct an analysis comparing the full ITT population of MOR-005 QW-QW and the patients from MorCAP1 in addition to a further analysis of the patients from the MAA and the full MOR-001 population. In both instances, the ERG recommended complete case analyses should be conducted and then the feasibility of subsequent PSM analyses should be explored. The ERG notes that in their response to TE, the company has submitted only a two year complete case analysis for the MAA and for MorCAP1. The ERG is concerned that there is still substantial clinical heterogeneity in the datasets the company has used. In particular, the ERG is unclear why the company has chosen to use MorCAP1 rather than the full MOR-001 trial population.

MorCAP1 comprises a subset of the MOR-001 trial population who have been matched to the MOR-004 study entry criteria in terms of baseline age (≥5 years) and 6MWT (≥30 and ≤325 metres). However, these restrictions were not applied to patients entering the MAA and the ERG notes that [redacted]. The ERG therefore considers the full MOR-001 population should have been used in the company's complete case analysis.

The ERG is also concerned by the clinical heterogeneity that still remains in the MAA dataset despite the complete case analysis. This is because the ex-trial patients baseline for the complete case analysis has been taken as the point of entry to the MAA rather than the start of treatment with ESA. The ERG considers that the data for ex-trial patients should have used their baseline as the start of their original trial or treatment with ESA and for the two year complete case analysis (CCA) their follow-up should be for the timepoint 2 years from this baseline irrespective of their start date in the MAA. The ERG's concern around this is discussed further in Section 0, where Issue 5 and timepoints are covered. The ERG notes that the company has provided subgroup analyses of the MAA for the 2 year CCA separately for the treatment naïve and ex-trial populations and so the ERG considers the treatment naïve subgroup to represent the most reliable source of clinical effectiveness data for ESA.

A further concern of the ERG is the [redacted]. The ERG considers this to be of importance due to the dependency of the company's economic model on wheelchair status. The ERG also notes that even if the full MOR-001 population were considered for the 2 year CCA [redacted] The ERG has therefore conducted an exploratory 1 year CCA using the full MOR-001 population and the MAA treatment naïve population. For completeness, the ERG also provides a summary of the company's 2 year CCA below.

The ERG 1 year CCA used all patients from MOR-001 and the MAA treatment naïve populations with data at baseline and 12 months for the respective outcomes. The ERG took the decision to conduct the CCA based on individual outcomes rather than requiring patients to have complete data for every outcome and this therefore means there is heterogeneity between the populations used for each of the outcomes. However, the ERG considers this to be the best approach to maximise the available data given the large reduction in patients numbers for the CCA when only patients deemed to be complete cases for all outcomes are included ([redacted] patients in the MAA for one year CCA of

6MWT, FVC, wheelchair status and EQ-5D composite score compared with up to [redacted] patients when a complete case is required for individual outcomes; MOR-001 not checked due to time constraints). The ERG considers it important to highlight that the ERG 1 year CCA is consistent in this respect to the company's 2 year CCA.

The ERG notes that in the company response to TE, the company has done a large amount of work to clean the data and has also contacted clinicians to try to obtain missing data. However, the ERG noted during its analyses that the individual patient data file supplied by the company [redacted]

The company reported that there was no imputation for missing data in any of their analyses. The ERG considers this to be reasonable given the heterogeneity of patients with MPS IVA.

The company conducted 2 year CCAs using the whole MAA population as well as separately for the treatment naïve and ex-trial cohorts. In addition, the company conducted 2 year CCAs for the MorCAP1 subgroup of MOR-001. The outcomes considered by the company were wheelchair status, 6MWT, FEV1, FVC, EQ-5D-5L and response (based on 6MWT), although the ERG notes that EQ-5D-5L data were only available from the MAA patients. The ERG also notes that results reported by the company for FEV1 were limited to t-test analysis results and that FVC is of greater importance as it was included in the economic model. The ERG 1 year CCA thus does not include FEV1.

The results of ERG and company analyses are discussed in parallel below. The ERG notes that the company provided baseline characteristics for patients in it's 2 year CCAs that included weight and sex (Tables 21 to 33 of the company report). The ERG notes that mean baseline weight [redacted] The ERG also notes that FVC was not collected in [redacted] Baseline characteristics from the patients in the ERG analyses are not presented due to time constraints but there is likely to

be clinical heterogeneity in the patients in the analyses. In addition, the ERG considers it important to highlight [redacted]

3.1.1 Results of the Company 2 year CCA and ERG 1 year CCA

In the ERG's analyses, the definition of wheelchair (WC) use has been based on that used in the company submission and so it is based on patients' answers to question 33 and question 33a on the MPS HAQ questionnaire. However, the ERG did not have access to the MPS HAQ questionnaire and therefore is unable to critique the suitability of the questionnaire for defining wheelchair status. The definitions of each wheelchair use category are as follows:

- Q33, if response is no to this question – no WC use;
- Q33a, if response is the first 3 options (1,2,3) – sometimes WC use;
- Q33a, if response is 4th option (always) – always WC use (or WC dependent).

3.1.1.1 6MWT

For inclusion in the ERG 1 year CCA of 6MWT, patients were required to have baseline wheelchair status in addition to data for 6MWT at baseline and 12 months. The ERGs 1 year CCA included [redacted] patients on ESA (MAA treatment naïve) and [redacted] patients for SoC (MOR-001). The results of the ERG's 1 year CCA show that there is [redacted] in the MAA treatment naïve cohort compared with MOR-001 (Table 2). The ERG considers it important to highlight that the always use wheelchair category comprised of [redacted]

Table 2. Mean 6MWT and mean change from baseline in 6MWT by baseline wheelchair status, Year 1 complete cases (CCA for 6MWT and all patients required to have baseline WC status), MOR-001 and MAA treatment naïve patients

Outcome by health state at baseline	MOR-001			MAA treatment naïve		
	Mean	SD	N	Mean	SD	n
Mean 6MWT at baseline (metres)						
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Some wheelchair use	[redacted]					
Always use wheelchair	[redacted]					
Pooled	[redacted]					
Mean 6MWT at 12 months (metres)						
No wheelchair use at baseline	[redacted]					
Some wheelchair use at baseline	[redacted]					
Always use wheelchair at baseline	[redacted]					
Pooled	[redacted]					
Mean change from baseline in 6MWT at 12 months (metres)						
No wheelchair use	[redacted]					
Some wheelchair use	[redacted]					
Always use wheelchair	[redacted]					
Pooled	[redacted]					
Percentage change from baseline in 6MWT at 12 months (%)[a]						
No wheelchair use	[redacted]					
Some wheelchair use	[redacted]					
Always use wheelchair	[redacted]					
Pooled	[redacted]					

[a] Percentage change from baseline in 6MWT was calculated using the aggregate mean data for each group rather than individual level data thus SD was not calculable.

Abbreviations: 6MWT, 6-minute-walk test; N/A, not applicable; SD, standard deviation, WC, wheelchair.

The company's 2 year CCA for 6MWT for the MAA was not broken down by baseline wheelchair category (Tables 52 to 54 of the company report). The results for the pooled MAA population showed that there was

[redacted]

The 1 year change from baseline in 6MWT for the treatment naïve cohort in the company analysis [redacted]

The results of the company's 2 year CCA for 6MWT for MorCAP1 show [redacted] from baseline of [redacted] m at 12 months and [redacted] m at 24 months (Table 47 of the company report). The results from the company's CCA of MorCAP1 suggest [redacted] in 6MWT at 1 year ([redacted] m) compared to the ERGs 1 year CCA of MOR-001 ([redacted]). However, the ERG notes from the data presented for MorCAP1 that there were [redacted]

3.1.1.2 FVC

The ERG's 1 year CCA for FVC included [redacted] As discussed earlier, patients aged under 5 years did not undergo assessment of FVC in the MAA and the ERG notes that [redacted] in MOR-001 in this age group had FVC assessment. The ERG notes that there is [redacted] (note FVC has been measured in litres [L] and so the ERG considers differences of 0.5 or higher to be clinically meaningful). [redacted]

The ERG considers the results of the 1 year CCA for FVC to show [redacted] Additionally, the ERG [redacted]

Table 3. Mean FVC and mean change from baseline in FVC by baseline wheelchair status, Year 1 complete cases (6MWT CCA and WC status at baseline), MOR-001 and MAA treatment naïve patients

Outcome by health state at baseline	MOR-001			MAA treatment naïve		
	Mean	SD	N	Mean	SD	N
Mean FVC at baseline (litres)						
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean FVC at 12 months (litres)						
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in FVC at 12 months (litres)						
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage change from baseline in FVC at 12 months (%)						
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Percentage change from baseline in 6MWT was calculated using the aggregate mean data for each group rather than individual level data thus SD was not calculable.

Abbreviations: FVC, forced vital capacity; N/A, not applicable; SD, standard deviation.

The results of the company's 2 year CCA for FVC comprised of [redacted]

[redacted]

3.1.1.3 Treatment response

The company conducted an analysis of treatment response using 6MWT in their definition of response. Based on the advice of clinical expert, the ERG considers both FVC and 6MWT to be important in determining treatment response to ESA. The ERG has thus conducted an analysis of treatment response using both 6MWT and FVC in the definition. In the ERG analyses of response patients were defined as either "responders" or "decliners" based on the following criteria:

- Responders: patients whose 12-month 6MWT and/or FVC result (depending on analysis; see Table 4 for results) was greater than or equal to their result at baseline (note: responders also include stable patients);
- Decliners: patients whose 12-month 6MWT and/or FVC result (depending on analysis; see Table 4 for results) did not equal or exceed their baseline score.

The ERG analysis of response defined as improvement or stabilisation in both FVC and 6MWT included [redacted] patients from the MAA treatment naïve cohort and [redacted] patients from MOR-001. Nevertheless, the results show [redacted]

[redacted]

Table 4. Response status, Year 1 complete cases, MOR-001 and MAA treatment naïve patients.

Outcome	MOR-001			MAA treatment naïve		
	N	%	N	n	%	N
6MWT						
Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decliners	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVC						
Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decliners	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6MWT and FVC						
Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decliners	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: %, percentage; 6MWT, 6-minute-walk test; FVC, forced vital capacity; MAA, managed access agreement.

The company analyses of treatment response classified patients as either long term responders or mild decliners. The ERG considers these definitions misleading as the responder category also included stable patients and there was no restriction on decline in 6MWT applied to the mild decliner category. The results of the company's 2 year CCA for 6MWT treatment response at 2 years (Tables 67 to 70 of company report) showed [redacted] The ERG notes that the number of responders in the company 2 year CCA [redacted]

3.1.1.4 EQ-5D-5L

As noted earlier, EQ-5D-5L data were not collected in MOR-001 and therefore data are only available for elosulfase. The ERG's 1 year CCA for EQ-5D-5L composite utility score comprised of [redacted] patients from the MAA treatment naïve cohort. The ERG considers the results [redacted]

[redacted]

Table 5. EQ-5D-5L scores by wheelchair status at baseline, Year 1 complete cases, MAA treatment-naïve patients

Health state at baseline	EQ-5D-5L at baseline, mean (SD)	EQ-5D-5L at 12 months, mean (SD)	EQ-5D-5L, mean change from baseline, mean (SD)	n
No use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
Some use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L, EuroQol five dimensions five levels; MAA, managed access agreement; SD, standard deviation.

The results of the company's 2 year CCA for EQ-5D-5L are reported as mean values with no corresponding baseline scores reported and the ERG is unclear whether the wheelchair status relates to wheelchair use at baseline or at 2 years (Tables 64 to 66 of company report). The ERG assumes that the results reported in Tables 64 to 66 of the company report relate to the mean EQ-5D-5L scores at 2 years and notes that they show

[redacted]

3.1.1.5 Wheelchair status

The ERG's 1 year CCA for wheelchair status comprised of [redacted] patients from MOR-001 and [redacted] patients from the MAA treatment naïve subgroup. The ERG notes that for both MOR-001 and the MAA treatment naïve populations,

[redacted]

[redacted]The ERG also notes that the company's model is based on wheelchair use and that change in wheelchair use as the main measure of disease progression in MPS IVA was a concern expressed by the HST committee in HST2 (discussed further in Section 3.7).[1]

Table 6. Change in wheelchair status from baseline to Year 1 for MOR-001 patients (one year CCA)

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total number of patients (N=95)
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

Table 7. Change in wheelchair status from baseline to Year 1 for MAA treatment naïve patients (one year CCA)

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total number of patients (N=36)
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

The results of the company's 2 year CCA for change in wheelchair status are reported across Tables 34 to 45 of the company report and included results for the transition from baseline to year 1, baseline to year 2 and year 1 to year 2 for the MAA pooled population, MAA ex-trial subgroup, MAA treatment naïve subgroup and MorCAP1 population. The ERG notes that there were [redacted] patients in the MAA analysis of which [redacted] were ex-trial patient and [redacted] were treatment naïve. For MorCAP1, there were [redacted] patients in the analyses of change in wheelchair status and [redacted] of these started in the always use wheelchair category.

[redacted]

[redacted]

3.1.2 *Additional information and analyses provided by the company*

In the company response to TE, the company provided a scatterplot of EQ-5D-5L and FVC to assess correlation between these variables (Figure 4, company report). However, the ERG notes that the company plotted the data for each timepoint (baseline, 1 year and 2 years) on the same scatterplot with [redacted] The ERG therefore does [redacted]

The company also reported that pairwise Student's T-tests were conducted to determine whether changes from baseline and differences between patient populations (MAA/MAA ex-trial/MAA treatment naïve and MorCAP1) were statistically significant for the outcomes of 6MWT, FVC and FEV1 in their 2 year CCAs . As discussed earlier, the ERG does not consider the comparison of the MAA data with MorCAP1 to be appropriate and the ERG is concerned about the [redacted] in the company's 2 year CCA of the MAA and therefore the ERG does not discuss the results of the pairwise Student's T-tests.

The ERG also notes that the company has presented a series of patient case studies and cited clinical expert opinion in their response to TE. While the ERG appreciates that these suggest positive benefits with ESA that extend beyond the clinical outcomes assessed in the statistical clinical analyses, they are nevertheless subjective. The ERG considers it important to highlight them so that the committee can consider how to make best use of them for its decision making.

3.2 Issue 2: Use of elosulfase alpha treatment regimens that are not consistent with the recommended dose in the European Union marketing authorisation (2.0 mg/kg/QW) at treatment initiation in some of the ex-trial 'managed access agreement' patients

The MAA comprised of [redacted] patients, of which [redacted] were ex-trial patients and the trials from which the patients originated from were:

- MOR-002 (n=[redacted]);
- MOR-004/005 (n=[redacted]);
- MOR-006 (n=[redacted]); and
- MOR-007 (n=[redacted]).

The ERG notes that in only MOR-006 and MOR-007 were all patients commenced on the EU marketing authorisation recommended dose of ESA of 2.0 mg/kg/week (QW). The patients in MOR-002 instead received 12 weekly escalating doses of ESA starting at 0.1 mg/kg/QW and transitioning to 1.0 mg/kg/QW then 2.0 mg/kg/QW. Patients could then receive a further 12 weeks treatment on the 1.0mg/kg/QW dose before entering MOR-100 and receiving the 2.0mg/kg/QW ESA dose again.

Patients in MOR-004/005 could have received either placebo, ESA 2.0 mg/kg/every other week or ESA 2.0mg/kg/QW for the initial 24 weeks of MOR-004. Those who entered MOR-005 would have received either ESA 2.0 mg/kg/every other week or ESA 2.0mg/kg/QW for between 36 and 96 weeks before transitioning to Part 2 of MOR-005, where all patients received the 2.0mg/kg/QW dose of ESA.

The ERG notes that it is unknown which patients from MOR-004/005 continued into the MAA and that the results of MOR-004 showed that the patients on the ESA 'weekly' treatment regimen had a greater mean change in 6MWT from baseline compared to those on the 'every other week' ESA treatment regimen (mean 36.5m, standard deviation [SD] 58.5; and mean 14.9, SD 40.8, respectively). The ERG thus considers the inclusion of ex-trial patients from MOR-004/005 and MOR-002 in the MAA population would likely bias results against ESA; although due to the use of inconsistent timepoints since treatment commencement with ESA the ERG does not consider it possible to predict the resulting direction of bias in the company's 2 year CCA. The ERG's concern around timepoints is discussed further in Section 0.

The ERG notes that the company's 2 year CCA of the MAA ex-trial patients showed [redacted] from MAA baseline compared to the MAA treatment naïve patients (Tables 53 and 54 of company report) [redacted] in FVC (Tables 59 and 60 of company report). However, the ERG also acknowledges that the removal of patients from MOR-002 and removal of those who did not consistently receive the weekly 2.0mg/kg dose of ESA in MOR-004/005 would reduce the number of patients in the ex-trial population. Nevertheless, the ERG considers a sensitivity analysis to explore the impact of dose is required along with the use of data timepoints commencing from baseline prior to treatment with ESA to enable a robust assessment of the effectiveness of ESA. The ERG approach to focus its 1 year CCA on the MAA treatment naïve patients overcomes the issues of inconsistent ESA dose and timepoints.

3.3 Issue 3: Absence of a systematic literature review to identify studies for standard of care

In the ERG report it was discussed how the company had not reported details of how the MOR-001 study was identified and selected as the best source of data to inform SoC in the CS. The ERG was therefore concerned about the robustness of the company's methods for selecting MOR-001 and could not be certain as to whether alternative more appropriate sources of data have been omitted. The ERG recommended that a full systematic literature review (SLR) was conducted to identify studies for SoC. The ERG noted that in the CS an SLR was conducted to identify studies of ESA.

In the company response to TE, the company reported that they updated their earlier SLR that had previously focused on studies of ESA to allow the identification of studies published on SoC between 2019 and June 2021 (earlier SLR for ESA was conducted in November 2019 and updated in November 2000). For the update, the ERG notes that only terms for MPS IVA were included in the search strategies with no restrictions based on study design or intervention. However, date limits were applied to restrict the findings to studies indexed in the databases from 2019 onwards. The ERG considers this to be an extremely restricted SLR as any studies indexed prior to 2019 for SoC would still not be identified. The ERG notes that the company reported their updated SLR did not identify any new studies of relevance to SoC suitable for inclusion in the economic model. However, the ERG remains concerned about the absence of an SLR to search for studies prior to 2019 and cannot be certain that MOR-001 is the best source of data to inform SoC for the comparison with ESA in the MAA study. Additionally, the company's reporting of their findings from this updated SLR did not adhere to PRISMA reporting guidelines and reasons for exclusion of studies was not clearly

documented. Due to time constraints the ERG has been unable to review the 11 studies identified by the company as reporting on, "*the incidence and/or longitudinal outcome in patients with MPS IVa*" and yet not deemed to be relevant for informing data or model inputs related to SoC.

The ERG also considers it important to highlight that the company reported in their response to TE that they couldn't perform a *de novo* full systematic literature review due to time constraints. Additionally, the company reported that if new studies providing data were identified it may have required a fundamental change to the model structure. Nevertheless, the ERG considers the absence of a full SLR for SoC means the uncertainty around the best source of data still remains.

3.4 Issue 4: Clinical heterogeneity in the clinical analyses and inappropriate methods for handling of missing data

The ERGs clinical experts' advice was consistent with information from the company in reporting that MPS IVA comprises a heterogenous patient population. The ERG is thus concerned that individual patients could have markedly different baselines and treatment responses. In the company submission (CS), the company compared the mean estimates of patients observed at each time point and did not account for the fact that these represent different cohorts of patients with potentially very different outcomes. The company has now conducted a 2 year CCA which means that the patients with data at baseline, one year and two years for a particular outcome are all the same group of patients. The ERG considers this helps to address the issue of clinical heterogeneity in the company's analyses. However, as already discussed in Section 3.1, in both the company and ERG CCAs, each outcome represents a different cohort of patients with potentially very different outcomes. This is because the CCA was done on an outcome basis rather than requiring patients to have complete case data for all outcomes. As discussed in Section 3.1, despite the flaws of this approach, the ERG considers it the best way of maximising the available data on ESA and SoC. Ideally the CCA would be done using only patients with data for all outcomes, but the ERG considers that this approach would lead to even smaller patients numbers and so the results would be less reliable. However, the ERG also considers it important to highlight that many of the outcomes are likely to be correlated (e.g. 6MWT, FVC and wheelchair use) and so it is not ideal to review each outcome independently.

Additionally, the clinical heterogeneity between the SoC patients and ESA patients remains in both the company and ERG CCAs [redacted] (see Section 3.1 for further detail). The ERG notes that this is not unexpected given

both the heterogenous nature of MPS IVA and that the treatments are informed by unmatched patients from two separate clinical studies (MOR-001 and the MAA, respectively). The ERG considers that ideally a PSM should be conducted to match the MAA and MOR-001 patients for each outcome. However, because of time constraints neither the company nor the ERG were able to conduct propensity score matching (PSM) analyses for any of the outcomes. The ERG also considers it important to highlight that the use of PSM would further limit the number of patients in any of the analyses and so the results for each treatment may be less reliable albeit the populations are more comparable.

The ERG notes that the company reported in their response to TE, that in their 2 year CCA:

"the MorCAP1 population was used, which has less heterogeneity than the overall MOR-001 population, as it applied the inclusion criteria for the MAA to the MOR-001 population in order to create a pseudo-comparator arm which similar characteristics to the MAA patients (age ≥ 5, 6MWT at baseline of ≥30m and < 325m)."

However, the ERG considers this to be an inappropriate approach as the inclusion criteria of the MAA did not restrict patients in the MAA by age or baseline 6MWT. Additionally, the ERG notes [redacted] The ERG also notes that the baseline demographic tables in Section 2.3.1.3 of the Company report from 27.08.21 shows that [redacted] As discussed in Section 3.1, the ERG does not agree with the company's use of MorCAP1 to inform SoC for the comparison with ESA from the MAA dataset. The ERG instead considers it would be more appropriate to compare the full MOR-001 population with the MAA population. The ERG therefore considers caution should be used when drawing conclusions about the effectiveness of SoC compared to ESA from the company's 2 year CCA.

In addition, the ERG considers it would be useful to see a CCA of the MOR-005 QW-QW ESA patients and that for these patients a CCA of MorCAP1 would be the most appropriate source of data for SoC. The feasibility of PSM for this analysis should also be explored.

3.5 Issue 5: Use of inconsistent timepoints within and between studies for assessment of clinical outcome data

In the ERG report, the ERG noted that inconsistent timeframes were used to inform the clinical analyses at set timepoints (Year 1, Year 2, Year 3, etc.) presented in the CS. In particular, for MOR-

001, the ERG noted that the data used to inform the Year 1 change from baseline could have been collected [redacted] after the baseline visit. In addition, the ERG had concerns that [redacted]

The company reported in their response to TE that they had addressed this issue by the reassignment of timepoints with further details provided in their report dated 27.08.21. The ERG notes from the company report that patients in MOR-001 were reassigned to timepoints that matched the timepoints for each outcome of relevance in the MAA. The ERG considers the company to have provided detailed data around the reassignment of timepoints for patients in MOR-001 including histograms and tables that show [redacted]% of patients were reassigned to timepoints that were within 2 months of the true data. The ERG considers this to be a vast improvement in the data structure compared to in the company submission and that the timepoints between the MAA treatment naïve cohort and the MOR-001 patients are now much more consistent. However, the ERG still has concerns around the use of the ex-trial patient data in the MAA.

The ERG notes that the baseline for the ex-trial patients in the MAA is classed as their baseline on entry to the MAA rather than their baseline at trial entry or commencement of ESA in their original trial. This therefore means that ex-trial patients have received treatment with ESA prior to entry to the MAA and in some patients this may have been several years of treatment, thus the baseline is not consistent with that of the treatment naïve patients. The impact of this discrepancy at baseline in the MAA is unclear and therefore the ERG considers the data from the ex-trial patients should be reanalysed to utilise the baseline as being prior to commencement of ESA. Additionally, the data for the one year and two year timepoints should reflect one and two years of treatment with ESA, respectively rather than the time since baseline in the MAA. Unfortunately the ERG did not have access to the original trial baseline data for the MAA ex-trial patients and so the ERG was unable to conduct any exploratory analyses to assess the impact of this.

[redacted] (Section 3.1.1). The ERG therefore took the decision to restrict its analyses to the treatment naïve cohort of the MAA (please see Section 3.1 for further detail and results from the ERGs exploratory analyses).

3.6 Issue 6: Clinical data used in the model

The company's two-year CCA of the MAA and of MorCAP1 still has substantial clinical heterogeneity. In particular, the ERG is unclear why the company has chosen to use MorCAP1 rather than the full MOR-001 trial population.

The ERG is also concerned by the clinical heterogeneity that still remains in the MAA dataset despite the CCA. This is because for the ex-trial patients, the baseline for the CCA has been taken as the point of entry to the MAA rather than the start of treatment with ESA. A further concern is the [redacted] The ERG considers this to be of importance due to the dependency of the company's economic model on wheelchair status. The ERG has therefore conducted an exploratory 1-year CCA using the full MOR-001 population and the MAA treatment naïve population (see Section 3.1 and 3.5 for more details and for results of the ERG's analysis).

3.7 Issue 7: Company's modelling approach

The company's modelling approach did not change after TE. The company maintained its view that WC use is the best available outcome to measure patients' functioning and quality of life (QoL). The company investigated the relationship between respiratory function (FVC) and quality of life, and reported that no correlation was identified.

The company's analysis consisted of plotting EQ-5D-5L scores against corresponding FVC measures at baseline, 12 months and 24 months (Figure 4 of the company's resubmission). The company reported that 48 patients were part of the CCA for both outcomes in the MAA data and that no statistical analysis was conducted. The ERG has several concerns around the company's analysis. Firstly, the number of patients included in this analysis was 16 (not 48 as reported by the company), with 3 data points in time, hence 48 observations. Secondly, the company plotted all the observations together, for the different time points, therefore without any analysis of the trend over time. Thirdly, the company used the entire MAA population, which as discussed in Section 3.1 is not appropriate (and should have been restricted to treatment-naïve patients).

The ERG analysed the mean EQ-5D-5L and the mean FVC observed for the same 16 patients at baseline; 12 months; and 24 months, separately for each time point, and concluded that the mean EQ-5D-5L score increased at every time point [redacted] respectively) as did FVC [redacted] respectively). Even though a robust conclusion cannot be derived by simply

looking at the mean values over time, these suggest a positive trend between the increase in QoL and FVC.

Importantly, the ERG originally pointed to the Lampe *et al*. 2015 study, which concluded that in adults with MPS IVA, endurance (6MWT) and pulmonary function (FVC) measures showed a strong and statistically significant correlation with patients' EQ-5D-5L. After TE, the company replied that the Lampe *et al*. 2015 study was conducted in a small population (24 patients) of German patients and that the most relevant source of UK data (the MAA dataset) provided different conclusions. The ERG notes that the company's additional analysis was based on fewer patients than the Lampe *et al*. 2015 study and did not provide any statistical analysis. In their re-submission, the company explicitly stated that, "*No statistical tests were performed using wheelchair status outcomes or EQ-5D-5L"*.

Additionally, MOR-005 found that impaired respiratory function (measured by FVC and FEV) is one of the leading causes of morbidity and mortality in MPS IVA patients. The study (sponsored by BioMarin) suggested that ESA slowed down, and partially reversed, the natural progression of respiratory dysfunction associated with MPS IVA over a 2-year period. The ERG, therefore, notes again, that a model based on respiratory outcomes would have more appropriately captured disease progression, and possibly the impact of ESA.

The ERG concludes that it has not seen any new data on the relationship between patients' QoL and FVC or WC outcomes to mitigate its original concerns around the company's modelling approach.

The ERG also notes the HST2 evaluation consultation document report and the committee's concerns around having a WC-based model: "*The Committee* [...] *heard from the clinical and patient experts that the categories of wheelchair use in the clinical trials could have been subjective. They emphasised that patients use wheelchairs in different ways, to manage endurance and daily activities according to their individual needs, so the effect of treatment is not necessarily well represented by this measure. Furthermore, patients do not judge their quality of life by how much they are using the wheelchair. The Committee considered that this evidence was informative but was mindful of putting too much emphasis on it. "* and *"The Committee concluded that the key determinants of mortality are the respiratory and cardiac complications, and that what matters the most to people with the condition is the ability to carry out normal everyday activities with sufficient endurance and without pain or fatigue*."

Another subsisting ERG concern is that 6MWT measures at baseline in the MAA dataset provide inconsistent and implausible representations of the modelled WC categories chosen by the company. As a response to TE, the company reported that WC inputs had been revised to reflect the new CCA in the MAA data. The ERG considers it important to emphasise that transition probabilities across WC states in the model after year 1 were dependent on patients' change in 6MWT and FVC scores (and not on WC data).

In the company's updated model, the values reported in Table 8 were used to re-estimate the time that SoC patients take to transition from the no wheelchair use (NWC) to the sometimes wheelchair use (SWC) state and from the SWC state to the wheelchair dependent (WCD) state. The ERG has several concerns with the estimation of these values to be used as WC thresholds in the model – the company reported to have pooled the baseline, 12-month and 24-month mean 6MWT observed in each time point to estimate the 6MWT value attributable to each WC category in MorCAP1. The ERG disagrees with "pooling" (which the ERG interpreted as taking the average across the 3 timepoints) across time as to do so reflects disease progression as time goes by for untreated patients but also reduces the sample size considerably (see Table 8). Furthermore, the results lack face validity as patients progressing from the NWC to the SWC state have an increase of [redacted]m in their 6MWT.

Even though the company reported that all of these new thresholds were used in the model, this is incorrect. Given the (implausible) increase needed in 6MWT for patients to progress from the NWC to the SWC state, the company has instead assumed that SoC patients had a [redacted] probability of progressing from the NWC to the SWC state of the model, every year (after year 1) of the model. This assumption is unsubstantiated and is biased in favour of ESA patients, who were assumed to have a [redacted] probability of transitioning from the NWC state to the SWC state in the model.

Equally important, the inconsistency in the WC thresholds defined in the company's model and the underlying clinical data remains. For example, the threshold used in the company's model of 46m to exit the SWC state (and entering the WCD state) is not consistent with the baseline 6MWT in MOR-001 ([redacted]).

In the ERG's additional investigation of the 1-year CCA of MOR-001 (described in Section 3.1), the baseline data in MOR-001 and in the MAA treatment-naïve patients (reported in Table 9) for 6MWT values have face validity as the distance walked by patients in the 6MWT decreases as patients' WC dependency increases. The ERG notes the marked differences in the MOR-001 and in the MAA mean

6MWT values at baseline, which make the definition of entrance and exit thresholds for WC categories impossible to be defined in such a way that is consistent with the underlying clinical data simultaneously for both studies. This, once more, reinforces the ERG's view that a model based on WC use is unlikely to be fit for the purpose of decision making.

As a scenario analysis, and to provide an alternative to the company's unsubstantiated assumptions, the ERG used the MOR-001 6MWT values at baseline to re-define the entrance and exit thresholds for each WC state in the model ([redacted] as the mean NCW distance; [redacted] to exit the NWC state; and [redacted] to exit the SWC state). The ERG acknowledges the additional uncertainty in the WCD state threshold, given that it was based on [redacted] patients. The ERG analysed the mean 6MWT distance in the WCD category for all patients in MOR-001 with available 6MWT and WC data at baseline and arrived at [redacted] ([redacted] patients). Therefore, the ERG conducted and additional scenario analysis where [redacted] were assumed instead of [redacted]. The details of this analysis are further discussed in Section 3.8 and results are provided in Section 4.

Table 8. Mean 6MWT by wheelchair status reported by the company for MorCAP1

Health state	Mean 6MWT	n
No wheelchair use	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]

Table 9. Mean 6MWT by wheelchair status, 1-year CCA, MOR-001 and MAA treatment-naïve patients

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

With regards to FVC outcomes, the company did not use the re-analysed data in the model and kept the assumption that the mean FVC level at which patients become wheelchair dependent (as a result of disease progression) is 1L.

The ERG's 1-year CCA of FVC outcomes are reported in Table 10. As discussed in Section 3.1, the FVC values lack face validity. The ERG also points to the discrepancy in FVC mean values in MOR-001 and the MAA treatment naïve patients. The ERG notes, once more, that this shows the poor correlation between WC status and disease progression.

FVC measures were only used to determine patients' movements from the WCD state to the paraplegic state. The company's assumption was that patients entering the WCD state had an FVC of 1L, which is only [redacted] the mean value reported in Table 10 for the MOR-001 population. Therefore, the ERG did not change this assumption in the model.

Table 10. Mean FVC (L) by wheelchair status, 1-year CCA, MOR-001 and MAA treatment-naïve patients

Outcome by health state at baseline	MOR-001			MAA treatment naïve		
	Mean	SD	N	Mean	SD	n
Mean FVC at baseline (litres)						
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Percentage change from baseline in 6MWT was calculated using the aggregate mean data for each group rather than indiivual level data thus SD was not calculable.

Abbreviations: FVC, forced vital capacity; N/A, not applicable; SD, standard deviation.

Conclusion on company's modelling approach

The ERG concludes that there is evidence in literature to support a strong correlation between endurance and mobility measures (6MWT and 3-minute stair climb [3MSC]) and patients respiratory measures (FVC) with patient's EQ-5D-5L/HRQoL. Furthermore, there is also a study pinpointing mobility as the key determinant for HRQoL in patients with MPS IVA.[2] The same study concluded that HRQoL reduces dramatically if patients become WCD, while small increases in mobility leading

to less use of a WC greatly improves HRQoL, although the ERG could not ascertain how the different levels of WC dependency were defined or captured in the study.

Given the thresholds for change in WC use defined by the company in the model are contradictory to the clinical outcome data observed at baseline in the MOR-001 and the MAA datasets, and the discrepancy in baseline 6MWT and FVC values between MOR-001 and the MAA patients in the same WC categories, the ERG cannot support the use of the company's economic model to assess the relative costs and benefits of ESA. The ERG also notes that the change in WC use is the driver of the economic results.

The ERG considers that a model based around endurance and respiratory measures would have provided a better tool for decision making. Crucially, such a modelling approach would have allowed the company to use the MAA or the MOR-005, and MOR-001 data to estimate the decrease (or increase) in 6MWT and FVC outcomes according to treatment arm, instead of relying almost solely on assumptions around disease progression. The ERG notes that WC use data from the MOR-001 and the MAA studies are only used in the first year of the economic model, while progression in the subsequent years was based on assumptions for the ESA arm, and on 6MWT and FVC outcomes from MOR-001 for the SoC arm. Therefore, the company had to make further assumptions to link FVC and 6MWT outcomes to the WC states in the model, where the outcome data could have been directly used.

3.8 Issue 8: Estimation of WC dependency in the model

Given the availability of annual WC change data, the ERG did not agree with the company's original approach of using the data on WC change from baseline to 72 weeks in the MAA dataset and from baseline to 2 years in the MOR-001 study, respectively, to model the transition between WC states in the first year of the model.

The company did not change its approach after TE and used the CCA from baseline to year 2 in the MAA and in MorCAP1 to estimate the transition probabilities (TPs) from baseline to year 1 of the model, using the 2-year CCA data. The ERG disagrees with this use of these data and due to the issues discussed in Section 3.1, the ERG replaced these in the model with the TPs from baseline to year 1 in the MAA (treatment naïve patients) and in MOR-001 using the ERG's 1-year CCA.

Table 11 and Table 13 report the TPs used by the company in the model, for ESA and SoC patients, respectively. Table 12 and Table 14 present the TPs derived from the ERG's 1-year CCA.

For ESA, the main difference is the probability of patients remaining in the NWC use state ([redacted]% in the company's model vs [redacted]% in the MAA analysis). The other difference resides on the probability of patients remaining in the SWC state ([redacted]% in the company's model), while the MAA data show that [redacted]% of patients progressed from being SWC to WCD. For SoC, the main difference is the company's assumption that all patients stay in the same state, where in MOR-001, most patients progressed or improved their WC status from baseline to year 1. Results of the ERG's analysis using the 1-year CCA TPs in the model are provided in Section 4.

Table 11. Transition matrices for baseline to Year 1 used in the model, MAA patients, treatment-naive

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
*sum of the probability of patients transitioning from the NWC state to the SWC (36%) and to the WCD (9%) states.			

Table 12. Transition matrices for baseline to year 1, CAA by 1 year, MAA patients, treatment-naïve

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total number of patients (N=36)
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

Table 13. Transition matrices for baseline to Year 1 used in the model, MOR-001

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair
No wheelchair use	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]
*company's assumption			

Table 14. Transition matrices for baseline to Year 1, CCA by 1 year, MOR-001

FROM ↓ TO →	No wheelchair use	Some wheelchair use	Always use wheelchair	Total number of patients (N=97)
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]

The distribution of patients at the end of year 1 in the ESA arm of the model is a key model driver, given the company's assumption that at the end of year 1 in the model there is a probability of [redacted] of patients progressing to the next (more dependent) WC state in the model for the remaining of their lifetime. Mathematically, this assumption is the equivalent of assuming that only 1 in [redacted] patients changes WC dependency per year.

The ERG's original concerns around this assumption remain. The ERG has not seen any data to substantiate the company's assumption that ESA patients do not progress after year 1 in the model. This assumption also implies that ESA patients' 6MWT and FVC values at year 1 do not change for these patients' lifetime, as 100% of ESA patients were considered to be "long-term responders" by the company at year 1.

The company also kept the assumption that after year 1 in the model, SoC patients in the NWC and the SWC states lose 6.84m in their 6MWT annually[3] (until they reached the exit thresholds of the WC states). Patients in the WCD and paraplegic states were assumed to lose 0.1L in FVC every year, and once they reached 0.3L FVC in the model they move to the end-of life state. The ERG's original concerns around the use of the estimates used to derive the increase in WC dependency for SoC patients remain.

The 6.84m decrease in 6MWT reported in Harmatz *et al*. was that of the matched population to the MOR-005 study, and not for the ITT population. The annual decrease seen in the ITT population in the study was 4.86m (instead of 6.84).[3] The ERG, originally recommended that:

1. The value used to estimate the change in 6MWT outcomes for SoC patients was taken from the re-analysis of MOR-001;
2. The value used was based on the available annual estimate (similar to what has been requested for changes in WC use).

Furthermore, the company did not provide a justification for using the 6MWT decline for SoC patients from the Harmatz *et al.* 2013, while ignoring the increase in FVC of 2.44% in total FVC (L) per year (ITT population) for the same patients in the study.

As discussed in Section 3.1, the ERG calculated the 1-year change in 6MWT (Table 15) and FVC (Table 16) outcomes in MOR-001 and in the MAA treatment-naïve patients. Both the company's 2-year CCA and the ERG's 1-year CCA show increases in 6MWT and in FVC outcomes for ESA and SoC patients. Given the company's model structure, which used SoC patients' decrease in 6MWT and FVC outcomes over time to estimate disease progression, it is difficult to implement the MAA and the MOR-001 results in the model, as originally requested by the ERG.

In order to incorporate the clinical data from the studies in the economic analysis, the ERG conducted a scenario analysis where the following assumptions where made:

1. Entrance and exit thresholds in the WC states in the model were re-estimated as described in Section 3.7.
2. Patients' relative changes in 6MWT ad FVC from MOR-001 and the MAA were used to estimate SoC and ESA patients' 6MWT and FVC values at the end of year 1 in the model, respectively. For example, given that NWC patients in the model were assumed to start with a 6MWT of [redacted] (see Section 3.7), at the end of year 1, SoC patients had a mean 6MWT of [redacted], while ESA patients had a mean 6MWT of [redacted] (see Table 15).
3. After year 1 in the model and given the lack of robust long-term clinical data from MOR-001 and the MAA, the ERG assumed that ESA and SoC patients lose an annual 4.86m in their 6MWT as reported in Harmatz *et al*. for SoC patients. Given that ESA patients have higher 6MWT values at the end of year 1, it takes longer for ESA patients to progress to the more dependent WC state. For example, it takes ESA patients 25 years to transition from the NWC to the SWC category, while the same transition takes 13 years for SoC patients (see Table 17).
4. After year 1 in the model, the ERG kept the company's assumption that patients lose an annual 0.1L FVC. Nonetheless, the ERG assumed that both SoC and ESA patients suffered the same loss, albeit departing from different FVC thresholds. Given that the 1-year CCA showed SoC patients in the WCD category to have an increase in FVC, while ESA patients had a decrease in FVC in the same category (see Table 16), in the ERG's calculations it takes longer for SoC patients to progress to the paraplegic state than ESA patients (see Table 17). Even

though this assumption reflects the observed data, the ERG acknowledges that it might not reflect a clinically plausible scenario. Therefore, the ERG conducted an alternative scenario analysis where SoC and ESA WCD patients are assumed to have the same mean FVC at the end of year 1 (see Table 17).

The ERG undertook an additional scenario analysis where it was assumed that ESA had an effect every year in the model, as long as patients were on treatment. Given the lack of data to substantiate any estimate of long-term effectiveness, the ERG caveats its analysis and notes that the results should be interpreted with caution. For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). This assumption was based on the pooled results reported in Table 15, which show that ESA patients had an improvement of [redacted] in their 6MWT compared to SoC patients after year 1. For example, when this is assumed in the model, it takes ESA patients 77 years to progress from the SWC to the WCD state, compared to 35 years in the SoC arm (see ERG scenario 2 in Table 17). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). Results of the ERG's scenario analysis are reported in Section 4.

Table 15. Change in 6MWT, ERG's CCA by 1 year

Outcome by health state at baseline	MOR-001			MAA treatment naïve			Difference
	Mean	SD	n	mean	SD	n	
Mean change from baseline in 6MWT at 12 months (metres)							
No wheelchair use	[redacted]						
Some wheelchair use							
Always use wheelchair							
Pooled							
Percentage change from baseline in 6MWT at 12 months (%)							
No wheelchair use							
Some wheelchair use							
Always use wheelchair							
Pooled							

Abbreviations: 6MWT, 6-minute-walk test; N/A, not applicable; SD, standard deviation.

Table 16. Change in FVC, ERG's CCA by 1 year

Outcome by health state at baseline	MOR-001			MAA treatment naïve			Difference
	Mean	**SD**	**n**	**mean**	**SD**	**n**	
Mean change from baseline in FVC at 12 months (litres)							
No wheelchair use	[redacted]						
Some wheelchair use	[redacted]						
Always use wheelchair	[redacted]						
Pooled	[redacted]						
Percentage change from baseline in FVC at 12 months (%)							
No wheelchair use	[redacted]						
Some wheelchair use	[redacted]						
Always use wheelchair	[redacted]						
Pooled	[redacted]						

Abbreviations: FVC, forced vital capacity; N/A, not applicable; SD, standard deviation.

Table 17. Years to disease progression after year 1 in company's model and ERG's alternative estimates

Outcome by health state at baseline	MOR-001			MAA treatment naïve			
	Company's model	**Estimated by the ERG**	**ERG's alternative scenario1**	**Company's model**	**Estimated by the ERG**	**ERG's alternative scenario1**	**ERG's alternative scenario2**
Years taken to change from NWC to SWC	[redacted]						
Years taken to change from SWC to WCD	[redacted]						
Years taken to change from WCD to paraplegic	[redacted]						

*using the alternative 73m exit threshold for the WCD state

^assuming the same as SoC

The ERG's analysis uses the 1-year data available from the MAA and the MOR-001 studies, which shows an increase in 6MWT outcomes for ESA patients from baseline to year 1. After year 1, the ERG could not make any assumptions on the drug's effectiveness, given the lack of robust data. All the CCA by 2 years reported in the company re-submission show that ESA patients could still progress in their WC dependency from year 1 to year 2, therefore the ERG notes, again, the clinical implausibility in the company's assumption that there is a 0.0001 probability of ESA patients progressing after year 1 in the model.

The scenario analysis undertaken by the ERG still assumes a benefit associated with ESA, as patients take longer to progress from the NWC and the SWC categories than SoC patients. The ERG caveats its analysis by the fact that the model assumes a constant loss in patients' 6MWT over time whereas both the MAA and the MOR-001 1-year CCA have shown an increase in patients' 6MWT. Nonetheless, the ERG notes that the model structure revolved around the assumption that patients' 6MWT decreases over time, and it is not possible to account for increases in this outcome in the model.

The ERG undertook two alternative scenarios around patients' FVC – one that uses the data observed in the MAA and in MOR-001, which suggests that WCD patients on ESA had poorer outcomes than SoC patients; and the other scenario which assumes that ESA has no effect on patients' FVC after 1 year of treatment. This assumption is substantiated by the data reported in Table 16, where overall, ESA patients had an increase in 0.06L in FVC over SoC patients after 1 year of treatment. Again, the ERG caveats its analysis by the fact that the model assumes a constant loss in patients' FVC over time, whereas both the MAA and MOR-001 1-year CCA; and MOR-005 have shown an increase in patients' FVC (for both SoC and ESA patients). Nonetheless, the ERG notes that the model structure revolved around the assumption that patients' FVC decreases over time, and it is not possible to account for increases in this outcome in the model.

The results of the ERG's analysis are reported in Section 4.

The company has not addressed multiple other concerns raised by the ERG originally. These are discussed below.

Asymptomatic state

Patients starting the model in the asymptomatic state were assumed to have an annual probability of progression to the NWC (also considered the "symptomatic" state) of 28.3% in the SoC arm. This

estimate was based on the assumption that SoC patients take 3 years to become symptomatic. The company based this assumption on the Montaño *et al*. study.[4]

Asymptomatic patients on ESA were assumed not to progress in the first year of the model, and to have a probability of progression of [redacted] in the subsequent years. This estimate was based on the company's clinical experts' opinion that it would take patients on ESA an additional 5 years (so a total of 8 years) to become symptomatic, compared to SoC patients.

The ERG notes that the Montaño *et al*. study reported that the mean age of onset of disease was 2.1 years, with initial symptoms recognised between 1 and 3 years.[4] Therefore, the ERG conducted a scenario analysis where SoC patients take 2 years to become symptomatic.

Before TE the ERG noted that patients on ESA were assumed not to progress from the asymptomatic state during the first year of the model. This meant that the company's assumption of a 5-year delay on patients becoming symptomatic was actually a 6-year delay when compared to SoC patients. More importantly, this delay in patients becoming symptomatic was based on clinical expert opinion and according to the ERG's clinical experts, even though a delay in the onset of symptoms could be possible, there is no evidence to suggest that such delay would translate into 5 or 6 years. Therefore, the ERG originally asked the company to conduct a scenario analysis where this delay associated with ESA was removed from the model and provides the results in Section 4.

Paraplegic and end-stage states

During the first year of the model, patients could transition from the asymptomatic or NWC states to the paraplegic state as a result of unsuccessful cervical fusion surgery. In the following years, patients could progress from the WCD and the paraplegic states into the end-stage state, where patients were assumed to always be in a WC and require continual mechanical ventilation as their FVC threshold reached 0.3L or less.

The ERG found an error in the economic model as patients in the NWC state were being given a probability of cervical fusion of 0% instead of the 38% intended by the company (for example, please see cell BS14 in "PF_comparator_Sym" tab, where the "p_FusionOP_Sometimes" needs to be replaced with "p_FusionOP_never" in the formula). The ERG requested that the company corrected this error during TE, however the company has not changed this in the model. The ERG did not have time to correct this in the model.

3.9 Issue 9: Estimation of mortality

The majority of the ERG's concerns around the estimation of mortality in the model were not addressed by the company during TE.

In the company's base case analysis, mortality for patients treated with ESA was assumed to be the same as that of the general population matched for age and sex. The relative risk (RR) of mortality for SoC patients was assumed to be 2.38 greater than the general population mortality. The company based its assumption on Quartel *el al*. 2018, a 15-year study of MPS VI patients treated with galsulfase. The study showed that 24% of patients treated with galsulfase had died after 15 years of treatment, while 57% of treatment-naïve patients had died over the same period. The company used these data to estimate the RR of death as 2.38 (57%/24%) and applied it to the ESA patients' mortality to estimate mortality for SoC patients.

Clinical expert opinion provided to the ERG informed that for a mild form of MPS IVA, patients treated with ESA could live to be around 50 or 60 years old. However, there are [redacted]% of ESA patients alive at 95 years old in the company's post-TE model. This suggests a clinically implausible scenario and an overestimation of survival in the model.

The ERG's clinical experts also disagreed with the company's assumptions that ESA patients experience the same mortality as the general population matched for age and sex. This was considered clinically implausible as many of the complications of MPS IV that cause death are not normalised by ESA, such as cardiac valvular disease, cervical spinal compromise, chest deformities (which cause restrictive lung disease), and tracheal obstruction.

Furthermore, the company is underestimating the mortality observed in the Quartel *et al*. 2018 study. Their research in MPS VI patients treated with galsulfase, shows that the 5-year mortality rate for MPS VI ERT-treated patients was 12.5%. This compares to 0.03% estimated by the company for ESA patients in the model (matched for age). Furthermore, at the end of the 15-year follow up period in the Quartel *et al*. 2018 study, there were about 65% of ERT patients alive and 40% of SoC patients alive, while in the company's model there were 99% of ESA patients alive after 15 years of treatment and 77% alive in the SoC arm.

The ERG advised that if the company wanted to use the Quartel *et al.* 2018 study to estimate mortality in the model post-TE, the company should use the 15-year Kaplan-Meier survival data observed for ERT-treated and SoC patients in the same study in their analysis (as the company's

approach clearly overestimates the survival observed for both treatment arms in Quartel *et al*. 2018). The company did not undertake the analysis proposed by the ERG.

As a scenario analysis, the company originally estimated mortality as consequence of decreased %FVC in the model. The ERG notes that in the company's updated model post TE, (similar to the model provided post-clarification), this scenario was not working; therefore, the ERG had to correct its implementation in the model.

Average baseline values of %FVC were assigned to the different WC states in the comparator arm of the model based on the mean absolute baseline FVC values reported in MOR-001. The ERG found several discrepancies in the baseline input values used by the company therefore, the ERG re-analysed the %FVC predicted values in MOR-001, using the company's updated dataset.

The % FVC values were then obtained for each patient by dividing the absolute FVC values at baseline by the predicted FVC value, which was calculated according to the recommendations by the European Respiratory Society and by using the reference equation of European Community for Steel and Coal (Quanjer *et al.* 1993). The ERG provides the re-estimated values in Table 18.

To estimate the impact of ESA on %FVC (and thus, on mortality) the company used an improvement factor of %FVC vs baseline of [redacted] over the course of 3 years of treatment with ESA. The company reported the source of the improvement factor to be the MOR-002/100 trial, where the percent change in FVC for the MOR-002 population was captured over 72 weeks, followed by an additional 72 weeks of percent change in FVC data in the extension study MOR-100.

By applying the [redacted] improvement on SoC %FVC values, the company estimated the %FVC values for ESA. Finally, the company assumed that for every 10% decrement in FVC compared to 100% predicted FVC there was a RR for mortality of 1.12.[5] The company then applied the resulting RR to the general population mortality to estimate deaths per health state, per treatment arm.

The ERG's concern with the use of the [redacted] improvement factor remains. MOR-100 was an extension study with patients from MOR-002, where all patients took part in dose escalation (ESA 0.1 mg/kg/QW for weeks 1-12, 1.0 mg/kg/QW for weeks 13-24 and 2.0 mg/kg/QW for weeks 25-36 and then 2.0 mg/kg/QW in MOR-100). The choice of MOR-100 was not justified by the company and introduces additional clinical heterogeneity in the model population given the dose escalation regimen and the difference in baseline population when compared to the MAA study. The ERG

originally recommended that the company analysed the improvement factor in FVC over time observed in MOR-005 and applied in this scenario (as this was the ERG's preferred data to be used to estimate FVC). The company did not undertake such analysis. Therefore, the ERG used the FVC improvement reported in Table 16 , based on the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients of [redacted]%)

Finally, the company assumed that for every 10% decrement in FVC compared to 100% predicted FVC there is a RR for mortality of 1.12. This estimate was reported to be taken from the Neas and Schwartz 1988 study. As originally pointed out by the ERG, the right estimate to be taken from the study was 1.15 and not 1.12. The company reported undertaking this scenario but did not report the results, only that it did not affect the final ICER. The ERG conducted this scenario and presents the data used in Table 18. Results of the ERG's analysis are reported in Section 4.

Table 18. Decrease in %FVC and mortality risk per WC state, per treatment arm

Wheelchair state	Predicted FVC		Resulting relative risk for mortality (based on 1.15 per 10% decrement)
	Baseline	**Decrement from 100%**	
Standard of care arm			
Asymptomatic	80%	20%	1.32
No wheelchair use	25%	75%	2.85
Sometimes use wheelchair	20%	80%	3.05
Wheelchair dependent	16%	84%	3.23
Paraplegic	16%	84%	3.23
Elosulfase alpha arm			
Asymptomatic	80%^	20%	1.32^
No wheelchair use	31%*	69%	2.62
Sometimes use wheelchair	25%*	75%	2.85
Wheelchair dependent	20%*	80%	3.05
Paraplegic	20%*	80%	3.05

* these values were estimated by applying the [redacted]% improvement on SoC %FVC baseline values
^ assumed the same as SoC

Finally, the ERG notes that a scenario linking the change in FVC to mortality is the ERG's preferred approach to estimate survival in the model, as the latter relies on fewer assumptions than the company's base case and links, to some extent, the underlying clinical FVC data used in the model (in the ERG's analysis) to the estimation of mortality.

3.10 Issue 10: Estimation of quality of life in the model

The company changed the assumption that the utility associated with each WC state in the model differed by treatment arm, as requested by the ERG before TE. The company also updated the utility values used in the model to reflect the CCA of utility data in the MAA.

The company kept the treatment specific utility increment associated with an increase in 6MWT and in FVC outcomes for the ESA arm. The increment was calculated using regression data reported in Lampe *et al.* 2015, which showed a 0.002 QALY gain for a 1m increase in 6MWT and 0.2 QALY gain for 100m gain; and a 0.2 QALY gain for a 1L increase in FVC for adult patients. The company changed the mean gain in 6MWT in the ESA arm (from 60m in the original model to 90.7m) in the updated model and kept the increase in mean FVC (0.054L) to derive the utility increment.

Therefore, for the 90.7m gain in 6MTW assumed for ESA patients, the company estimated a utility increment of [redacted] QALYs and of [redacted] QALYs associated with the gain of 0.054L in FVC. The 0.18 additional QALY gain was added to the NWC and SWC health states, and the 0.01 increase was added to WCD and the paraplegic states in the ESA arm. A full list of the utility values used in the SoC arm, the treatment specific increments, and the utility values used in the ESA arm in the company's base case are show in Table 19.

Table 19. Model utility values

Health state	Utility value at baseline in MAA dataset, ERT-naïve patients and used in SoC arm in the original model	Utility value at baseline in CAA MAA dataset, ERT-naïve patients and used in SoC arm in the updated model	Treatment specific increment	Utility value used in ESA arm updated model	Utility value used in ESA arm original model
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Wheelchair dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: SE, standard error; Soc, standard of care; ESA, elosulfase alpha *assumed the same as the WCD state ^assumed the same as the utility for end stage disease in the SoC arm					

The ERG notes its original concern with the inconsistency in the company's rationale as it argues a weak correlation between EQ-5D and FVC outcomes to justify having a WC based model; however, it argues for a strong correlation between FVC outcomes and EQ-5D outcomes to apply a utility increment to patients' utilities while receiving ESA.

The ERG is concerned with the updated utility values used by the company to estimate QoL for SoC patients ([redacted]; [redacted]; [redacted] for NWC; SWC; and WCD, respectively). The values used are meant to be those collected at baseline for the treatment-naïve patients from the MAA CCA; however, the ERG is unclear how these were estimated. The company used the values reported in Table 6 of the company's resubmission which were described as being, "*generated for all observations across wheelchair states; three times the observations were available as there were complete cases (complete cases multiplied by the number of observations per case)*." Therefore, the ERG does not consider that the values used by the company correspond to baseline utility values.

The ERG did some additional investigation of the MAA treatment-naïve data, using the maximum available baseline data (i.e. including all patients with baseline EQ-5D and WC data), and arrived at the values reported in Table 20, which are considerably lower than those used by the company in their updated model.

The utility values used in the HST2 (which in turn where taken from the Hendriksz *et al*. 2014[2] burden of disease study for patients with MPS IVA), were 0.846; 0.582; and 0.057 respectively, in adults (18 years or above) not using a wheelchair, using a wheelchair only when needed, and always using a wheelchair. The same study reported values of 0.534, 0.664 and –0.180, respectively, in children (7-17 years).

The ERG notes that the Hendriksz *et al*. 2014 utility value for WCD adults is [redacted] from that observed in the MAA analysis; however, the WCD and the SWC values in the Hendriksz study

are [redacted], for both adults and children. Given the discrepancy in the MAA utilities and the Hendriksz study; the fact that the Hendriksz utilities were accepted in the HST2; and the higher number of adult patients in the published study across each WC category (4 for NWC; 12 for SWC; and 9 for WCD) when compared to the number of adults in the MAA treatment naïve patients (3 for NWC; 3 for SWC; and 2 for WCD - Table 20), the ERG decided to use the Hendriksz study to estimate the utilities for the SoC arm of the model.

Furthermore, given the mean age across the WC categories in the MAA reported in Table 20 (used in the model), and the limited time available for the ERG to conduct additional analysis, the ERG's preferred utility values are the ones reported in the Hendriksz study for adults. Ideally, children's utilities for the NWC and the WC states would have been used in the model for 1 year, and 3 years, respectively, until patients reached 18 years. Nonetheless, given the small number of years and the limited time available to the ERG to conduct additional analysis, the ERG decided that the use of adult utilities wasn't unreasonable.

In the analysis conducted by the ERG, the utility values for the paraplegic and end of stage patients remained the same as those in the company's analysis (0.057 and 0.024, respectively) as they were taken from the CS for HST2.

Table 20. Mean EQ-5D values by wheelchair status by maximum available baseline data, MAA treatment naïve patients

Health state	Mean utility	n	Mean age	n below 18 years	n above 18 years	n with unknown age
No wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Always use wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG disagrees with the 6MWT increase of 90m and with the increase of 0.054L in FVC associated with ESA assumed by the company to estimate the increase in utility values in the treatment arm. The ERG is not aware how these values were estimated, and the ERG's preference is to link the utility increments to the estimated relative treatment effectiveness for ESA. Using the 6MWT and the FVC relative gains discussed in Section 3.7, the ERG estimated the utilities for the ESA arm in the model as reported in Table 21. Results of the ERG's analysis are reported in Section 4.

Table 21. Model utility values estimated by the ERG

Health state	Utility value used in the company's SOC arm of updated model	Utility value at baseline and assumed for the SOC arm in ERG's analysis (taken from Handriksz)	Effect of ESA on 6MWT (m) or FVC (L)	Treatment specific increment	Utility value used by the ERG in the ESA arm	Utility value used in ESA arm of company's updated model
Asymptomatic	[redacted]	1.000	-	-	1.000	[redacted]
No wheelchair	[redacted]	0.846	[redacted]	[redacted]	[redacted]	[redacted]
Some wheelchair	[redacted]	0.582	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	[redacted]	0.057	[redacted]	[redacted]	[redacted]	[redacted]
Paraplegic	[redacted]	0.057*	-	-	[redacted]	[redacted]
End state	[redacted]	0.024	-	-	0.024	[redacted]

Abbreviations: SE, standard error; SOC, standard of care; ESA, elosulfase alpha

*assumed the same as the WCD state

^assumed the same as the utility for end stage disease in the SoC arm

[a] assumed the same as the utility for NWC

Given the uncertainty around the improvement in quality of life for ESA patients compared to SoC patients discussed in Section 0, the ERG also conducted a scenario analysis where the utility increments associated with 6MWT and FVC were removed from the model. Results of the ERG's analysis are reported in Section 4.

3.11 Issue 11: Underestimation of treatment costs in the analysis

Elosulfase alfa is an intravenous drug administered weekly over four hours at a dose of 2mg per kilo of body weight. The list price per 5mg vial is £750; however, after TE the company agreed a patient access scheme discount of [redacted] per 5ml vial.

The company also re-estimated the baseline weight in every WC category according to the undertaken 2-year CCA. Therefore, the ERG re-estimated the mean baseline weight for asymptomatic patients based on the Montaño et al., 2008 paper, first reported by the company in their original submission, where it is reported that the mean weight of males and females with MPS IVA at 0 years is 3.59 kg; and 3.53 kg; respectively. The ERG weighted the mean weights by the

proportion of males (52%) and females (48%) in the model and arrived at the weight of 3.56 kg. The ERG also re-estimated patients' baseline weight to include the maximum number of patients in the MAA treatment naïve dataset with baseline weight and WC use data. The ERG arrived at a baseline weight of 19.8kg for NWC patients (n=13); 27kg for SWC users (n=18), and 35.2kg (n=2) for WCD patients.

Table 22 shows the baseline weight, respective number of vials and weekly costs estimated in the model.

The average baseline weight for the asymptomatic patients (12.3) remained the same as that used in the company's original submission, which had been taken from MOR-001. The ERG disagrees with this decision, particularly when the ERG could not trace the value used back to MOR-001 patients. Furthermore, given the baseline difference between the MAA and MOR-001 patients discussed throughout this report, the ERG also does not agree with using baseline characteristics from MOR-001 to represent ESA patients in the model.

Therefore, the ERG re-estimated the mean baseline weight for asymptomatic patients based on the Montaño et al., 2008 paper, first reported by the company in their original submission, where it is reported that the mean weight of males and females with MPS IVA at 0 years is 3.59 kg; and 3.53 kg; respectively. The ERG weighted the mean weights by the proportion of males (52%) and females (48%) in the model and arrived at the weight of 3.56 kg. The ERG also re-estimated patients' baseline weight to include the maximum number of patients in the MAA treatment naïve dataset with baseline weight and WC use data. The ERG arrived at a baseline weight of 19.8kg for NWC patients (n=13); 27kg for SWC users (n=18), and 35.2kg (n=2) for WCD patients.

Table 22. Dosing of elosulfase alfa by health state in the model

Health state	Average weight (KG)	Vials needed	Weekly cost with patient access scheme
Asymptomatic	12.30	5.00	[redacted]
No use wheelchair	17.56	8.00	[redacted]
Some use wheelchair	28.3	12.00	[redacted]
Wheelchair dependent	35.2	15.00	[redacted]

Abbreviations: KG, kilogram

The ERG remains concerned that patients' weight increase over time is not being considered in the model. The ERG estimated the relative increase in patients' weight from baseline to year 1 (to maximize the number of patients with data available for the analysis) or from baseline to year 2 in the case of WCD patients, as the latter did not have 12-month measures for weight. Table 23 shows that patients in the NWC, SWC, and WCD states increased in weight. The ERG applied the relative increase in weight reported in Table 23 to the baseline weight in the model to estimate patients' change in weight at year 1.

Given patients' age at baseline (14 years), it is likely that the company's assumption of constant weight throughout the model underestimates patients' weight in the long-term. This, in turn, leads to an underestimation of the treatment costs associated with ESA. Given the nature of MPS IVA, it's unlikely that patients' weight would progress similarly to that of the general population, nonetheless, assuming a constant weight throughout 100 years in the model is clinically implausible.

For the remainder of the model (i.e., after year 1) the ERG assumed that, on average, all patients would reach 36.7kg by the time they were 18 years old. This assumption was based on the Montaño *et al.*, paper[6] where it is reported that the mean weight of males and females with MPS IVA at 18 years is 37.6 ± 13.4 kg; and 35.8 ± 14 kg; respectively. The ERG weighted the mean weights by the proportion of males (52%) and females (48%) in the model and arrived at the weight of 36.7kg. The ERG then assumed that patients' weight would increase at a constant rate over the remaining years (from mean age at year 1 until they reached 18 years) and stopped when patients reached 36.7kg (see Table 24).

The ERG acknowledges that this scenario might still underestimate the future weight of patients in the model, and therefore the costs of ESA. Nonetheless, the limited time available to the ERG did not allow for a further investigation into the literature for weight predictions post 18 years in MPS IVA patients. The results of the ERG's analysis are reported in Section 4.

Table 23. Weight change in treatment naïve MAA patients estimated by the ERG, 1-year CCA for NWC and SWC and 2-year CCA for WCD

Health state	Average weight (KG) at baseline	n	Average weight (KG) at 12 months	n	Average weight (KG) at 24 months	n	Increase in weight
No use wheelchair	16.9	11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some use wheelchair	24.7	13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wheelchair dependent	50.4	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 24. Weight change applied by the ERG in the model

Health state	Average age at baseline (years)	Average weight (Kg) at baseline	Average weight (Kg) at 12 months (estimated)	Increase in weight until 18 years	Weight used in long-term model
Asymptomatic	0	3.6	4.2*	32.5	36.7
No use wheelchair	16	19.8	21.0	15.7	36.7
Some use wheelchair	14	27.0	29.3	7.4	36.7
Wheelchair dependent	22	35.2	41.2	-	41.2

*taken from Montaño *et al. 2018*

Administration costs

Before TE, the ERG had requested that the company replaced the £207 with the updated £213 cost of treatment administration in the model as the company did not change this estimate, despite stating so in their clarification answers. Therefore, the ERG has replaced this estimate in the model and presents the results in Section 4.

Furthermore, the ERG had recommended that the company provided further clarification on the resource use included in the cost for home infusions as the ERG could not validate the company's estimation of the cost of home infusion derived by subtracting 4 hours of nurse supervision time from the cost of home infusion. The company has not provided information to substantiate this value, therefore, the ERG cannot validate the company's estimation of a home infusion of £239.11.

Before TE, the ERG had requested that the company provided the following analyses/clarifications:

1. The ERG requested that the company provided the sources used for the costs for specialist care and palliative care, as the ERG has been unable to validate these in the reference cost schedule;
2. The ERG requested that the company provided a scenario analysis incorporating the ERG's clinical experts' proposed resource use for each WC category (reported in Table 44 of the ERG report).

The company did not comply with the ERG's requests. Therefore, the ERG conducted an additional scenario analysis using the resource use proposed by the ERG's clinical experts. The impact of the change in resource use on the final health state costs is provided in Table 25. Changing the resource use in the model had a negligible impact on the final ICER.

Table 25. Health state costs

Health state	Company base case cost	ERG clarification cost scenario
Asymptomatic	£227.10	£990.58
No use wheelchair	£628.21	£1012.43
Sometimes wheelchair	£906.50	£1132.60
Wheelchair dependent	£1471.71	£1299.58
Paraplegic	£1786.27	£1507.15
End stage	£3071.00	£7939.35

4 Results from ERG's exploratory analysis

In this section the ERG provides the results of the new exploratory analysis conducted after TE. The scenarios analyses conducted by the ERG are the following:

1. Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients.
2. Re-estimating the change in WC use in the model, which consisted of:
    - Using the MOR-001 6MWT values at baseline to re-define the entrance and exit thresholds for each WC state in the model ([redacted] as the mean NCW distance; [redacted] to exit the NWC state; and [redacted] to exit the SWC state).
    - Using the relative changes in 6MWT estimated from MOR-001 and the MAA (treatment-naïve patients) to calculate the changes in 6MWT values at the end of year 1 in the model, for SoC and ESA patients, respectively, per WC category.
    - Assuming that SoC and ESA patients have the same mean FVC at the end of year 1 in the WCD state.
    - Assuming, after year 1 in the model, that ESA and SoC patients lose an annual 4.86m in their 6MWT as reported in Harmatz *et al*. and also that ESA and SoC patients lose an annual 0.1L in their mean FVC.
3. Assuming that SoC patients take 2 years to become symptomatic.
4. Assuming that SoC and ESA patients take 2 years to become symptomatic (i.e., no difference in the two arms).
5. Estimating mortality using the company's modelling approach to link changes in FVC predicted to survival. The ERG re-calculated the %FVC predicted values in MOR-001 and assumed an improvement of FVC of [redacted]% associated with ESA as estimated in the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients. Finally, the ERG used the RR for mortality of 1.15 for every 10% decrement in FVC compared to 100% predicted FVC from the Neas and Schwartz 1988 study.
6. Using the utility values reported in the Hendriksz study for adults in the SoC arm, by WC state, and estimating utility increments for the NWC and the SWC utilities for the ESA arm, associated with the 6MWT increase of [redacted] and [redacted] (estimated by the ERG to be the increase in 6MWT results for NWC and SWC patients with ESA, respectively, as described in Section 3.10). For the WCD state, the ERG did not apply any utility increments in the ESA

arm, as there was no FVC increase observed for ESA patients in the ERG's analysis (see Section 3.10).

7. Replacing the mean baseline weight in the model to include the maximum number of patients in the MAA treatment naïve dataset with baseline weight and WC use data. The ERG arrived at a 19.8kg for NWC patients (n=13); 27kg for SWC users (n=18), and 35.2kg (n=2) for WCD patients. Assuming a baseline weight of 3.6kg for asymptomatic patients based on the Montaño *et al.* 2008 study.
8. Replacing the mean baseline weight in the model (as described in point 9) and using patients' weight at year 1 from the MAA to estimate the costs associated with ESA at year 1 in the model and assuming that on average, all patients would reach 36.7kg by the time they were 18 years old.
9. Replacing the £207 treatments administration cost in the model with the updated £213 estimate.

In addition to assumptions 1 to 9, the ERG ran the following alternative scenarios:

a) In point 2, using the alternative mean 6MWT distance in the WCD category for all patients in MOR-001 with available 6MWT and WC data at baseline [redacted] (instead of [redacted]).
b) In point 2, replacing the ERG's assumption that SoC and ESA WCD patients have the same mean FVC at the end of year 1 by the observed data from the MAA and MOR-001. Given that the 1-year CCA showed SoC patients in the WCD category to have an increase in FVC, while ESA patients had a decrease in FVC in the same category, in the ERG's calculations it takes longer for SoC patients to progress to the paraplegic state than ESA patients (see Table 17).
c) In point 6, assuming no utility increments associated with 6MWT and FVC for the ESA arm (and using the utility values reported in the Hendriksz study for adults to estimate the SoC and ESA utilities).

Results of the ERG's exploratory analyses are reported in Table 26 for the comparison of ESA with SoC, with the PAS for ESA included in the results. The key driver of the economic results remains the assumption made around the effect of ESA on patients' use of WC in the long-term. When the ERG used the improvements associated with ESA observed from baseline to year 1 in the MAA and in MOR-001, and assumed no further gains with ESA in the long-term, the ICER increased from [redacted] to [redacted] per QALY gained. The ERG notes that despite the assumption that ESA and SoC patients have similar progression in 6MWT scores after year 1 in the model, ESA patients have

higher 6MWT values at the end of year 1, thus, ESA patients take longer to progress to the more dependent WC states. For example, in the ERG's analysis it takes ESA patients 25 years to transition from the NWC to the SWC category, while the same transition takes 13 years for SoC patients (as discussed in Section 3.7).

The second key model driver is the long-term weight assumption made for patients in each WC category. When the ERG assumed that patients' weight changed over time, the ICER increased from [redacted] to [redacted] per QALY gained.

Finally, the third biggest key driver of the economic results is the inclusion of utility increments associated with 6MWT and FVC gains in the WC-related utilities for the ESA arm, followed by the fourth biggest driver – the method used to estimate mortality.

Table 26. Results of ERG's exploratory analysis with ESA's PAS

Scenario		Incremental costs	Incremental QALYs	ICER
0	Company base case	[redacted]	[redacted]	[redacted]
1	Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients.	[redacted]	[redacted]	[redacted]
2	Using the MOR-001 6MWT values at baseline to re-define the entrance and exit thresholds for each WC state in the model (270m as the mean NCW distance; 211m to exit the NWC state; and 28m to exit the SWC state). Using the relative changes in 6MWT estimated from MOR-001 and the MAA (treatment-naïve patients) to calculate the changes in 6MWT values at the end of year 1 in the model, for SoC and ESA patients, respectively, per WC category. Assuming that SoC and ESA patients have the same mean FVC at the end of year 1 in the WCD state. Assuming, after year 1 in the model, that ESA and SoC patients lose an annual 4.86m in their 6MWT as reported in Harmatz et al. for SoC	[redacted]	[redacted]	[redacted]

	patients and that patients lose an annual 0.1L FVC.			
3	Assuming that SoC patients take 2 years to become symptomatic.	[redacted]	[redacted]	[redacted]
4	Assuming that SoC and ESA patients take 2 years to become symptomatic (i.e., no difference in the two arms).	[redacted]	[redacted]	[redacted]
5	Estimating mortality using the company's modelling approach to link changes in FVC predicted to survival. The ERG re-calculated the %FVC predicted values in MOR-001 and assumed an improvement of FVC of [redacted]% associated with ESA as estimated in the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients. Finally, the ERG used the RR for mortality of 1.15 for every 10% decrement in FVC compared to 100% predicted FVC from the Neas and Schwartz 1988 study.	[redacted]	[redacted]	[redacted]
6	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state and using the 6MWT increase of [redacted] and [redacted] to estimate utility increments associated with the NWC and the SWC utilities for the ESA arm, respectively, and assuming a FVC increase of [redacted] to estimate the utility associated with the WCD state in the ESA arm.	[redacted]	[redacted]	[redacted]
7	Replacing the mean baseline weight in the model with 19.8kg for NWC patients (n=13); 27kg for SWC users (n=18), and 35.2kg (n=2) for WCD patients. Assuming a baseline weight of 3.6kg for asymptomatic patients based on the Montaño *et al.* 2008 study.	[redacted]	[redacted]	[redacted]
8	Replacing the mean baseline weight in the model and using patients' weight at year 1 from the MAA to estimate the costs associated with ESA at year 1 in the model and assuming that on average, all patients would reach 36.7kg by the time they were 18 years old.	[redacted]	[redacted]	[redacted]
9	Replacing the £207 treatments administration cost in the model with the updated £213 estimate.	[redacted]	[redacted]	[redacted]
a	Using the alternative mean 6MWT distance in the WCD category for all patients in MOR-001	[redacted]	[redacted]	[redacted]

	with available 6MWT and WC data at baseline [redacted] (instead of [redacted]).			
b	Assuming that SoC patients take longer to progress to the paraplegic state than ESA patients (to reflect the observed data in the MAA and in MOR-001).	[redacted]	[redacted]	[redacted]
c	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state (and assuming no utility increments associated with 6MWT or FVC measures for ESA).	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

The results of the combined exploratory analysis undertaken by the ERG are presented in Table 27. Depending on the assumption used to estimate WC exit and entrance thresholds; FVC progression over time for ESA patients; and including or excluding utility increments for ESA, the ERG's preferred ICERs range from [redacted] to [redacted] with ESA's PAS included.

Table 27. ERG's combined analysis with ESA's PAS

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
0	Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Using the updated WC TPs for year 1	[redacted]	[redacted]	[redacted]	[redacted]
1+2	Using the MOR-001 6MWT values at baseline to re-define the entrance and exit thresholds for each WC state in the model (270m as the mean NCW distance; 211m to exit the NWC state; and 28m to exit the SWC state). Using the relative changes in 6MWT estimated from MOR-001 and the MAA (treatment-naïve patients) to calculate	[redacted]	[redacted]	[redacted]	[redacted]

	the changes in 6MWT values at the end of year 1 in the model, for SoC and ESA patients, respectively, per WC category. Assuming that SoC and ESA patients have the same mean FVC at the end of year 1 in the WCD state. Assuming, after year 1 in the model, that ESA and SoC patients lose an annual 4.86m in their 6MWT as reported in Harmatz et al. for SoC patients and that patients lose an annual 0.1L FVC.				
1+2+3+4	Assuming that SoC and ESA patients take 2 years to become symptomatic (i.e., no difference in the two arms).	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3+4+5	Estimating mortality using the company's modelling approach to link changes in FVC predicted to survival. The ERG re-calculated the %FVC predicted values in MOR-001 and assumed an improvement of FVC of [redacted]% associated with ESA as estimated in the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients. Finally, the ERG used the RR for mortality of 1.15 for every 10% decrement in FVC compared to	[redacted]	[redacted]	[redacted]	[redacted]

	100% predicted FVC from the Neas and Schwartz 1988 study.				
1+2+3+4+5+6	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state and using the 6MWT increase of [redacted] and [redacted] to estimate utility increments associated with the NWC and the SWC utilities for the ESA arm, respectively, and assuming a FVC increase of [redacted] to estimate the utility associated with the WCD state in the ESA arm.	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3+4+5+6+7+8	Replacing the mean baseline weight in the model and using patients' weight at year 1 from the MAA to estimate the costs associated with ESA at year 1 in the model and assuming that on average, all patients would reach 36.7kg by the time they were 18 years old.	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3+4+5+6+7+8+9	Replacing the £207 treatments administration cost in the model with the updated £213 estimate.	[redacted]	[redacted]	[redacted]	[redacted]
Alternative **cumulative** ICERs (i.e., adding scenarios 1+2+3+4+5+6+7+8+9, and replacing assumptions where needed)					
a	Using the alternative mean 6MWT distance in the WCD category for all patients in MOR-001 with available 6MWT and WC data at	[redacted]	[redacted]	[redacted]	[redacted]

	baseline [redacted] (instead of [redacted]).				
b	Assuming that SoC patients progress slower than ESA patients to the WCD category (according to the MAA and MOR-001 data).	[redacted]	[redacted]	[redacted]	[redacted]
c	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state (and assuming no utility increments associated with 6MWT or FVC measures for ESA).	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

Finally, the results of the combined exploratory analysis with the alternative long-term assumption for the effectiveness of ESA undertaken by the ERG are presented in Table 28. This scenario assumes that the effect of ESA observed in the 1-year CCA would be observed for every year of treatment with ESA in the model. For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually).

Depending on the assumption used to estimate WC exit and entrance thresholds; FVC progression over time for ESA patients; and including or excluding utility increments for ESA, the ERG's preferred ICERs range from [redacted] to [redacted] with ESA's PAS included.

Table 28. ERG's combined analysis with ESA's PAS with alternative assumption for long-term effect of ESA

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
1+2+3+4+5+6+7+8+9	See Table 26	[redacted]	[redacted]	[redacted]	[redacted]

Alternative **cumulative** ICERs (i.e., adding scenarios 1+2+3+4+5+6+7+8+9, and replacing assumptions where needed)					
a	Using the alternative mean 6MWT distance in the WCD category for all patients in MOR-001 with available 6MWT and WC data at baseline [redacted] (instead of [redacted]).	[redacted]	[redacted]	[redacted]	[redacted]
b	Assuming that SoC patients progress slower than ESA patients to the WCD category (according to the MAA and MOR-001 data).	[redacted]	[redacted]	[redacted]	[redacted]
c	Using the utility values reported in the Hendriksz study for adults to estimate the SoC utilities associated to each WC state (and assuming no utility increments associated with 6MWT or FVC measures for ESA).	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

5 References

1. National Institute for Health and Care Excellence. Final evaluation determination: Elosulfase alfa for treating mucopolysaccharidosis type IVa [HST 2], 2015. Available from: https://www.nice.org.uk/guidance/hst2/documents/final-evaluation-determination-document. Date accessed: 23 Sept 2021.
2. Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. *Orphanet J Rare Dis* 2014; **9**: 32.
3. Harmatz PR, Mengel KE, Giugliani R, Valayannopoulos V, Lin SP, Parini R, et al. Longitudinal analysis of endurance and respiratory function from a natural history study of Morquio A syndrome. *Mol Genet Metab* 2015; **114**: 186-94.
4. Montaño AM, Tomatsu S, Gottesman GS, Smith M, Orii T. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. *J Inherit Metab Dis* 2007; **30**: 165-74.
5. Neas LM, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. *Am J Epidemiol* 1998; **147**: 1011-8.
6. Montaño AM, Tomatsu S, Brusius A, Smith M, Orii T. Growth charts for patients affected with Morquio A disease. *Am J Med Genet A* 2008; **146A**: 1286-95.

Vimizim NICE HST – Additional information request related to the company's preferred utility values

Elosulfase alfa for treating mucopolysaccharidosis type IVa (re-evaluation of HST2) [ID1643]

<table>
<tr><th>NICE request</th><th>Company response</th></tr>
<tr><td>Confirm whether baseline values were used from the treatment naive subgroup in the managed access data</td><td>No. Values used were mean of EQ5D composite score from 3 time points (baseline, 12M and 24M), for each wheel chair states (no wheelchair use, some wheelchair use, and wheelchair dependant). This was based on complete case analysis. So, number of observations will be 3 times the number of patients.</td></tr>
<tr><td>Provide an Excel spreadsheet with raw utility values that were used to estimate mean baseline utilities</td><td>The Excel workbook is attached. This workbook has 2 worksheets (EQ5D, DataFile).

The DataFile sheet lists all MAA records (as a proxy to indicate patients are treatment naïve, column K), and considers complete cases only (Those patients with complete record sets for year 1 and 2, Column HC).

EQ-5D is then average across the 3 time points (baseline, 12M and 24M) based on Wheelchair status at the specific time point (Column FK).

<table>
<tr><th>Live Table 66</th><th>EQ5D mean</th><th>EQ5D, SD</th><th>n</th></tr>
<tr><td>Pooled</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No use wheelchair</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Some use wheelchair</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Always use wheelchair</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td></tr>
<tr><td>Clarify how the mean values were estimated - the company said they took an average of 3 measures at each visit, but the ERG remains unclear of what these measures are</td><td>As explained above, this was calculated as mean of EQ5D composite score at 3 time points (baseline, 12M and 24M), for each wheelchair state (no wheelchair use, some wheelchair use, and wheelchair dependant). This was based on complete case analysis.</td></tr>
<tr><td>Explain why the ERG baseline values (reported in ERG's TE response and calculated from the company's raw data) are so different from the company's values (see</td><td>To our understanding, ERG in its review of the company response (dated September 2021), has used utility values from Hedriksz et al) for the standard of care arm. The company used utility values from MAA (Tx naïve) patients (mean of 3 time points for 3 wheelchair use states).</td></tr>
</table>

section 3.10 of the ERG critique of TE response, pages 37 to 40)	For the ESA arm, the company used the same utilities as in SOC arm, with utility increment associated with increment in 6MWT and FVC with ESA. The increment was calculated using regression data reported in Lampe et al. 2015, which showed a 0.002 QALY gain for a 1m increase in 6MWT and 0.2 QALY gain for 100m gain; and a 0.2 QALY gain for a 1L increase in FVC for adult patients.

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2)

ERG addendum post ECM1

October 2021

1 Introduction

This document provides the Evidence Review Group's (ERG's) addendum after the first committee meeting. The analyses provided in this addendum were requested by the NICE technical team.

2 Additional analyses requested by NICE

The NICE technical team requested ICERs that include the committee's preferred assumptions. The NICE technical team believe scenarios 4 and 5 are most likely to reflect committee's preferred ICER range. All the analyses requested by the NICE technical team include the following assumptions:

- Standard of care (SoC) patients that start in the asymptomatic state of the model are assumed to take 3 years to progress to the symptomatic state, while elosulfase alpha (ESA) patients take 9 years to move from asymptomatic to symptomatic;
- Use the ERG's scenario analysis linking mortality to decreased %FVC predicted in the model (with ERG's 1-year complete case analysis [CCA] estimations for FVC decrease taken from the MAA and MOR-001 data);
- Use the ERG's baseline utility data from the MAA for SoC patients and the ERG's estimations of FVC and 6MWT gains associated with utility increments in the ESA arm;
- The ERG's assumptions for changes in patients' body weight;
- Use a 3.5% discount rate.

The different scenarios requested by NICE (incorporating the assumptions described above) consist of the following:

Scenario 1:

- Company's approach with preferred assumptions described in section 2 above .

Scenario 2:

- Company's approach with preferred assumptions described in section 2 and with the assumption of a 4.86m (instead of a 6.84m) annual loss in 6MWT for SoC patients after year 1 in the model.

Scenario 3:

- Use of company's entrance and exit thresholds from the different WC categories in the model.
- Use the ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model.
- Assume a 4.86m and 0.1L losses in 6MWT and FVC measures, respectively, for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.

Scenario 4:

- Use the ERG's entrance and exit thresholds from the different WC categories in the model.
- Use the company's 2-year CCA WC transition data to model change in WC use from baseline to year 1 in the model.
- Assume a 4.86m and 0.1L losses for SoC patients after year 1 in the model and assume that that only 1 in 10,000 patients progresses per year in the ESA arm.

Scenario 5:

- Use the ERG's entrance and exit thresholds from the different WC categories in the model.
- Use the ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model.
- Use the ERG's estimated increase in 6MWT and FVC in the ESA & SoC arms from baseline to year 1 applied in the model according to the MOR-001 and the MAA data.
- Assume a 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.

Scenario 6:

- Use the ERG's entrance and exit thresholds from the different WC categories in the model.
- Use the ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model.
- Use the ERG's estimated increase in 6MWT and FVC in the ESA % SoC arms from baseline to year 1 applied in the model according to the MOR-001 and the MAA data.
- Assume a 4.86m and 0.1L losses for SoC patients after year 1 in the model and assume that the effect of ESA observed in the 1-year CCA would be observed for every year of treatment

with ESA in the model. For this scenario, the ERG assumed that after year 1, ESA patients lost 31% less than SoC patients in their 6MWT, (i.e., 3.3m vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost 4% less than SoC patients, (i.e., 0.0957L vs 0.1L, respectively, annually).

Table 1. Deterministic results (discounted except for life years gained)

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
1	Company's approach with preferred assumptions described in section 2	[redacted]	[redacted]	[redacted]	[redacted]
2	Company's approach with the assumption of a 4.86m (instead of a 6.84m) annual loss in 6MWT for SoC patients after year 1 in the model	[redacted]	[redacted]	[redacted]	[redacted]
3	•Company's entrance and exit thresholds from the different WC categories in the model •Use of ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model •ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.	[redacted]	[redacted]	[redacted]	[redacted]
4	•ERG's entrance and exit thresholds from the different WC categories in the model •Company's 2-year WC transition data to model change in WC use from baseline to year 1 in the model •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.	[redacted]	[redacted]	[redacted]	[redacted]
5	•ERG's entrance and exit thresholds from the different WC categories in the model •Use of ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model	[redacted]	[redacted]	[redacted]	[redacted]

	•ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.				
6	•ERG's entrance and exit thresholds from the different WC categories in the model •Use of ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model •ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that the effect of ESA observed in the 1-year CCA would be observed for every year of treatment with ESA in the model. For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost 31% less than SoC patients in their 6MWT, (i.e., 3.3m vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost 4% less than SoC patients, (i.e., 0.0957L vs 0.1L, respectively, annually).	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

The ERG highlights its concerns around the core assumptions included throughout these five scenarios:

- The assumption that SoC patients starting the model in the asymptomatic state take 3 years to progress to the symptomatic state, while ESA patients take 9 years to become symptomatic – the company based these assumptions on the Montaño *et al.* study for the SoC arm, and on clinical expert opinion for the ESA arm. The ERG notes that the Montaño *et al.* study reported that the mean age of onset of disease was 2.1 years, with initial symptoms recognised between 1 and 3 years. Therefore, the ERG considers that the correct estimate to use for SoC patients in the model is 2 years. Importantly, according to the ERG's clinical experts, even though a delay in the onset of symptoms for ESA patients could be possible, there is no evidence to suggest that such delay would translate into 6 years.

- The ERG received confirmation from the company post-TE that that the utility values used to estimate the utility for SoC patients ([redacted]; [redacted]; [redacted] for NWC; SWC; and WCD, respectively) in the company's model were not based on baseline utility values from the MAA dataset. The company confirmed that the utility values used in the SoC arm are those resulting from a "*composite score from 3 time points (baseline, 12M and 24M), for each wheelchair state*". Therefore, as discussed by the ERG in their response to TE, the ERG disagrees with the use of these utility data in the SoC arm as these reflect the impact of treatment with ESA on patients' quality of life over 2 years. In their response to TE, the ERG reported the results of its additional investigation of the MAA treatment-naïve baseline utility data, using the maximum available baseline data (i.e. including all patients with baseline EQ-5D and WC data), and arrived at the values [redacted] for NWC; SWC; and WCD, respectively.

  The ERG noted that the utility values used in the HST2 (which in turn were taken from the Hendriksz *et al*. 2014 burden of disease study for patients with MPS IVA), were 0.85; 0.58; and 0.06 respectively, in adults (18 years or above) not using a wheelchair, using a wheelchair only when needed, and always using a wheelchair. The ERG also noted that the Hendriksz *et al*. 2014 utility value for WCD adults are [redacted] from that observed in the MAA analysis; however, the WCD and the SWC values in the Hendriksz study are [redacted], for both adults and children. Given the discrepancy in the MAA utilities and the Hendriksz study; the fact that the Hendriksz utilities were accepted in the HST2; and the higher number of adult patients in the published study across each WC category (4 for NWC; 12 for SWC; and 9 for WCD) when compared to the number of adults in the MAA treatment naïve patients (3 for NWC; 3 for SWC; and 2 for WCD), the ERG decided to use the Hendriksz study to estimate the utilities for the SoC arm of the model. Nonetheless, the ERG also acknowledges the relevance of the scenarios provided in this addendum using the baseline utility data collected in the MAA in order to estimate the utility for SoC patients.

Finally, the ERG notes additional concerns around some of the scenarios requested by the NICE technical team. More specifically:

- The use of the company's entrance and exit thresholds from the different WC categories in the model – as discussed in the ERG's response to TE, the company's thresholds lack face validity (as patients progressing from the NWC to the SWC state have an increase of 77m in

their 6MWT) and were based on average values across the baseline, 12-month and 24-month mean 6MWT observed in each time point to estimate the 6MWT value attributable to each WC category in MorCAP1. The ERG noted the inconsistency in the WC thresholds defined in the company's model and the underlying clinical. For example, the threshold used in the company's model of 46m to exit the SWC state (and entering the WCD state) is not consistent with the baseline 6MWT in MOR-001 ([redacted]). Therefore, the ERG's preferred approach remains the use of the entrance and exit threshold re-estimated by the ERG.

- The use of the company's 2-year WC transition data to model change in WC use from baseline to year 1 in the model – given the availability of annual WC change data, the ERG does not agree with the company's approach of using the data on WC change from baseline to year 2 in the MAA and in MorCAP1 to estimate the transition probabilities from baseline to year 1 of the model. The ERG also disagrees with the company's methods of analysis used in the 2-year CCA (i.e. the use of the entire MAA population and of the MorCAP1 population as discussed in the ERG response to TE).
- The assumption that SoC patients in the NWC and the SWC states lose 6.84m in their 6MWT annually – the 6.84m decrease in 6MWT reported in Harmatz *et al*. was that of the matched population to the MOR-005 study, and not for the ITT population. The annual decrease seen in the ITT population in the study was 4.86m (instead of 6.84).
- The assumption that that only 1 in 10,000 ESA patients progresses per year, after year 1 in the model – the ERG has not seen any data to substantiate the company's assumption that ESA patients' 6MWT and FVC values at year 1 do not change for these patients' lifetime. The data in the CCA by 2 years reported in the company's submission show that ESA patients could still progress in their WC dependency from year 1 to year 2, therefore the ERG notes, again, the clinical implausibility in the company's assumption.

The ERG notes that its preferred ICER, making the most possible use of MAA data is based on the following assumptions:

- Assuming that SoC and ESA patients take 2 years to become symptomatic (i.e., no difference in the two arms).
- Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients.
- Using the entrance and exit thresholds estimated by the ERG.

- Assuming that after year 1 in the model, SoC patients lose 4.86m and 0.1L in their 6MWT and FVC outcomes, annually, and assuming that ESA has an effect every year in the model, as long as patients are on treatment. Given the lack of data to substantiate any estimate of long-term effectiveness with ESA, the ERG caveats its analysis and notes that the results should be interpreted with caution. For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). This assumption was based on the pooled results from the MAA and MOR-001, which show that ESA patients had an improvement of [redacted] in their 6MWT compared to SoC patients after year 1. For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 2, for ease of interpretation.
- Estimating mortality linking changes in FVC predicted to survival. The ERG re-calculated the %FVC predicted values in MOR-001 and assumed an improvement of FVC of [redacted]% associated with ESA as estimated in the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients.
- Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm, associated with the 6MWT increase of [redacted] and [redacted] (estimated by the ERG to be the increase in 6MWT results for NWC and SWC patients with ESA, respectively. For the WCD state, the ERG did not apply any utility increments in the ESA arm, as there was no FVC increase observed for ESA patients in the ERG's analysis.
- Using the ERG's assumptions for changes in patients' body weight.
- Replacing the £207 treatments administration cost in the model with the updated £213 estimate.

Table 2. Years to disease progression after year 1 in company's model and ERG's alternative estimates

Outcome by health state at baseline	SoC patients		ESA patients	
	Company's model	**ERG-preferred**	**Company's model**	**ERG-preferred**
Years taken to change from NWC to SWC	[redacted]	14	[redacted]	39
Years taken to change	[redacted]	35	[redacted]	77

from SWC to WCD				
Years taken to change from WCD to paraplegic	[redacted]	7.4	[redacted]	7.7

The resulting ERG-preferred ICER amounts to [redacted] per QALY gained, with incremental discounted costs and QALYs of [redacted], respectively, and incremental undiscounted QALYs of [redacted].

The ERG reiterates that the ICER of [redacted] assumes a life-long benefit associated with ESA, as patients take longer to progress from the all the WC states when compared to SoC patients. For example, as reported in Table 2, it takes ESA patients 77 years to progress from the SWC to the WCD state, compared to 35 years in the SoC arm; and 39 years vs 14 for patients to move from the NWC to the SWC states, respectively.

3 References

1. National Institute for Health and Care Excellence. Final evaluation determination: Elosulfase alfa for treating mucopolysaccharidosis type IVa [HST 2], 2015. Available from: https://www.nice.org.uk/guidance/hst2/documents/final-evaluation-determination-document. Date accessed: 23 Sept 2021.
2. Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. *Orphanet J Rare Dis* 2014; **9**: 32.
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6. Montaño AM, Tomatsu S, Brusius A, Smith M, Orii T. Growth charts for patients affected with Morquio A disease. *Am J Med Genet A* 2008; **146A**: 1286-95.