Common Drug Review
Clinical Review Report

July 2015

Drug	elosulfase alfa (Vimizim) (2 mg/kg of body weight)
Indication	For long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis IVA (Morquio A syndrome, or MPS IVA)
Listing request	As per indication
Manufacturer	BioMarin Pharmaceutical (Canada) Inc.

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ABBREVIATIONS

3MSCT	three-minute stair-climb test
6MWT	six-minute walk test
AE	adverse event
ATS	American Thoracic Society
ANCOVA	analysis of covariance
CDR	CADTH Common Drug Review
CI	confidence interval
ESA	elosulfase alfa
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GAG	glycosaminoglycan
GALNS	N-acetylgalactosamine-6-sulfatase
HAQ	Health Assessment Questionnaire
ITT	intention-to-treat
IV	intravenous
KS	keratan sulfate
LS	least squares
MCID	minimal clinically important difference
MPS	mucopolysaccharidosis
MPS IVA	mucopolysaccharidosis IVA; Morquio A syndrome
MVV	maximum voluntary ventilation
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation

EXECUTIVE SUMMARY

Introduction

Mucopolysaccharidosis IVA (MPS IVA), also known as Morquio A syndrome, is a rare autosomal recessive lysosomal storage disorder caused by mutations in the gene encoding for N-acetylgalactosamine-6-sulfate sulfatase (GALNS), the enzyme responsible for the catabolism of keratan sulfate (KS) and chondroitin-6-sulfate glycosaminoglycans (GAGs) found principally in skeletal and cartilaginous tissue.[1] As a result of this disorder, GAGs accumulate to toxic levels in lysosomes, producing widespread skeletal dysplasia, including short stature and various skeletal deformities.[1,2] The estimated incidence of MPS IVA in Canada is 0.38 to 0.5 per 100,000 live births, while at present, fewer than 100 patients with MPS IVA are estimated to be living in Canada.[3] The presentation and clinical course of the disease are highly variable, with severe and rapidly progressing forms typically presenting before the age of one year, moderate forms between one and five years, and attenuated or milder disease often diagnosed after the age of 20 years.[4] With more than 275 genetic mutations in the GALNS enzyme identified to date,[2] MPS IVA has been characterized as a disease of high genotypic and phenotypic heterogeneity.[5] It is a progressive disease, in which death typically occurs in the second or third decade of life in patients with severe disease; by comparison, patients with milder disease can survive into their seventies.[1] The cause of death is usually cardiorespiratory failure or spinal cord complications.

The definitive diagnosis of MPS IVA is established by enzymatic assay for GALNS activity in peripheral blood leukocytes.[6] In the absence of therapies specifically indicated in MPS IVA, the standard of care for the management of MPS IV has been palliative, using a combination of medical and surgical interventions for symptom management.[1,5] Frequent orthopaedic surgical interventions are often required to correct bone deformities.[2] Adjunctive pharmacotherapies used for symptom control include analgesics and bronchodilators.

Elosulfase alfa (ESA) (Vimizim) is a recombinant formulation of human GALNS, which is deficient in patients with MPS IVA. By replacing deficient GALNS, ESA is postulated to enhance the degradation and clearance of accumulated KS in patients with MPS IVA.[5] ESA is the first enzyme replacement therapy to be marketed in Canada for the treatment of MPS IVA. ESA is dosed at 2.0 mg/kg/week by intravenous (IV) infusion over four hours. ESA has a Health Canada indication as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS IVA. The manufacturer is seeking reimbursement in accordance with this indication.

The objective of this review was to evaluate the beneficial and harmful effects of ESA 2mg/kg IV once weekly as long-term enzyme replacement therapy in patients with MPS IVA.

Results and Interpretation

Included Studies

The evidence for this review was drawn from one phase 3 (MOR-004) double-blind, randomized (1:1:1), placebo-controlled trial comprising 176 patients aged five years or older with a confirmed diagnosis of MPS IVA. Patients were randomly assigned to either a weekly or alternate-weekly regimen of ESA 2.0 mg/kg or matching placebo for 24 weeks. This review considered only the weekly regimen of ESA, as this is the Health Canada–approved regimen.

Most (> 70%) of the patients studied were from Europe (44%) and North America (26%), which suggests that the trial data are generalizable to Canadian clinical practice. With more than 275 mutations identified in the GALNS gene thus far,[2] MPS IVA is a disease distinguished by substantial genotypic and phenotypic heterogeneity[5] and a highly variable clinical course. The MOR-004 trial appeared to be composed primarily of patients with intermediate or moderate disease, so there is some uncertainty regarding response to therapy in lesser and more severe phenotypes. However, the clinical expert consulted by the CADTH Common Drug Review (CDR) indicated that the studied population was reasonably reflective of patients with MPS IVA encountered in Canadian clinical practice.

Patient input received for this submission identified stabilization or slowing of disease progression as important outcomes, along with improved endurance and reduced morbidity associated with bone and joint disease. The primary efficacy outcome in MOR-004 was the change from baseline in the six-minute walk test (6MWT). At 24 weeks in duration, this trial provided relatively short-term efficacy data from an intermediate end point (6MWT) focused mainly on endurance that has not been validated in patients with MPS IVA (although it is considered by the FDA as an acceptable intermediate outcome for this population). There were limited or no data on other key clinical end points, including disease progression, survival, growth (in children), need for surgery, requirement for walking aids or wheelchairs, and quality of life.

Efficacy

A statistically significant increase in 6MWT was observed from baseline to week 24 favouring ESA (adjusted least squares [LS] mean difference: 22.5 m; 95% confidence interval [CI], 4.0 m to 40.9 m). However, interpretation of this result is complicated by the uncertain validity of the measure in MPS IVA and lack of a published minimal clinically important difference (MCID) in MPS diseases. Findings from urine KS, pulmonary function tests — i.e., forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and maximum voluntary ventilation (MVV) — as well as anthropometry (i.e., standing height, weight) and functional status as measured by the MPS Health Assessment Questionnaire (MPS HAQ) were either statistically non-significant or were not compared between treatments. Data on progression to wheelchair dependence were only reported descriptively and were largely uninformative.

Upon completion of MOR-004, most patients (98.9%) agreed to participate in an ongoing, open-label extension study called MOR-005, which was designed to run until either 240 weeks of treatment were completed or the study was terminated. In Part I of MOR-005, patients who received ESA treatment during MOR-004 continued to receive their same regimen (i.e., weekly or alternate-weekly ESA dosing), while patients who received placebo during MOR-004 were re-randomized to either a weekly or alternate-weekly regimen of ESA. In Part II, all patients were assigned to the weekly ESA regimen; this phase of the trial is ongoing and minimal data are available. The cohort of patients receiving weekly ESA throughout MOR-004 and into MOR-005 Part I appeared to maintain a similar 6MWT distance at week 48 as at week 24 in MOR-004. However, a limitation of these results was that data were available for less than 50% of the patients enrolled in MOR-005 Part I at 48 weeks.

Given the heterogeneity of the MPS IVA population with respect to underlying mutations and clinical presentation, it is likely that treatment response to ESA will also vary across patients. How clinicians will distinguish responders from non-responders is unclear; likewise, it is unclear under what circumstances, if any, ESA may be discontinued in the event of an equivocal response to therapy. Study MOR-004 is not informative in this regard.

Harms

Overall, adverse events (AEs) in MOR-004 were common, but not different in frequency between ESA and placebo (96.6% in both groups). The most common (> 10%) AEs with ESA treatment, which were more frequent than with placebo, were largely those considered to be infusion-associated reactions by the clinical expert consulted by CDR (although temporality AEs in relation to infusion of study drugs could not be determined from the available data); these included vomiting, pyrexia, headache, nausea, abdominal pain, diarrhea, oropharyngeal pain, otitis media, dizziness, dyspnea, gastroenteritis, and chills. The clinical expert further indicated that infusion-associated reactions are readily managed in a clinical setting, and would be expected to lessen with repeated exposure to therapy; however, tolerability over time was not specifically studied in MOR-004. Serious adverse events were more common with ESA treatment than placebo (15.5% versus 3.4%), with infections and infestations classified as serious adverse events occurring in 8.6% of patients in the ESA group and none in the placebo group. There were no withdrawals due to AEs and no deaths reported during the trial.

The safety profile in MOR-005 Part I appeared to be similar to that of MOR-004 in terms of tolerability and the type of AEs reported; no new safety signals were identified from these data.

Conclusions

In a single randomized controlled trial (RCT), ESA once weekly was shown to improve the primary efficacy outcome of change from baseline in 6MWT compared with placebo in patients aged five years and older with a confirmed diagnosis of MPS IVA. Although 6MWT is an accepted outcome for MPS IVA trials by regulatory authorities, the clinical importance of this result is unclear due to the lack of an MCID in MPS IVA, and uncertain association with outcomes of importance to patients with MPS IVA, such as pain, fatigue, mobility, disease progression, and the need for surgical intervention. Results were either not statistically significant, or statistical comparisons were not made for other outcomes of interest to this review, including the three-minute stair-climb test (3MSCT), urine KS, pulmonary function tests, anthropometry (e.g., height), requirement for wheelchair use, and measures of functional capacity. No data were available for quality of life, survival, or disease progression.

ESA treatment was more commonly associated with vomiting, pyrexia, headache, nausea, abdominal pain, diarrhea, oropharyngeal pain, otitis media, dizziness, dyspnea, gastroenteritis, and chills versus placebo. SAEs were more frequent with ESA treatment and most often classified as infections and infestations. There were no withdrawals due to AEs or deaths reported during the trial. No additional safety signals were identified from the data in the open-label extension trial (MOR-005).

TABLE 1: SUMMARY OF RESULTS

Outcome	MOR-004	
Key Efficacy Outcomes		
6MWT (m)	**ESA once weekly (n = 58)**	**Placebo (n = 59)**
N	57	59
Baseline, mean (SD)	203.9 (76.3)	211.9 (69.9)
Week 24 — change from baseline, mean (SD)	36.5 (58.5)	13.5 (50.6)
LS mean difference (95% CI)	22.5 (4.0 to 40.9)	
P value[a]	0.0174	
3MSCT (STAIRS/MIN)		
N	57	59
Baseline, mean (SD)	29.6 (16.4)	30.0 (14.1)
Week 24 — change from baseline, mean (SD)	4.8 (8.1)	3.6 (8.5)
LS mean difference (95% CI)	1.1 (–2.1 to 4.4)	
P value[a]	0.4935	
FVC (%)		
N	55	53
Baseline, mean (SD)	0.9 (0.5)	1.2 (0.9)
Week 24 — % change from baseline, mean (SD)	4.9 (12.0)	1.5 (14.2)
LS mean difference (95% CI)	3.3 (–3.1 to 9.6)	
P value[a]	0.3041	
FEV_1 (%)		
N	58	59
Baseline, mean (SD)	0.8 (0.4)	1.0 (0.7)
Week 24 — % change from baseline, mean (SD)	5.4 (11.5)	2.5 (16.8)
LS mean difference (95% CI)	1.8 (–5.5 to 9.2)	
P value[a]	0.6129	
MVV (%)		
N	49	50
Baseline, mean (SD)	28.3 (16.6)	34.8 (27.3)
Week 24 — % change from baseline, mean (SD)	10.8 (25.6)	2.4 (20.7)
LS mean difference (95% CI)	10.3 (–1.8 to 22.4)	
P value[a]	0.0943	
Safety Outcomes		
AEs		
n (%)	56 (96.6)	57 (96.6)

Outcome	MOR-004	
SAEs		
n (%)	9 (15.5)	2 (3.4)
WDAEs		
n (%)	0	0

3MSCT = three-minute stair-climb test; 6MWT = six-minute walk test; AE = adverse event; CI = confidence interval; ESA = elosulfase alfa; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ITT = intention-to-treat; LS = least squares; MVV = maximum voluntary ventilation; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] *P* value determined by t-test from ANCOVA model.

Note: ITT analysis set used for modelling LS mean difference; observed cases used for reporting group means. Baseline covariates adjusted in the model were age group (all presented outcomes); 6MWT category (all presented outcomes); continuous 3MSCT (for 3MSCT); FVC (for FVC); primary composite score — the average of component changes in normalized 6MWT, 3MSCT, and MVV from baseline measured at week 24 (for FEV_1) — and MVV (for MVV).

1. INTRODUCTION

1.1 Background on Condition

Mucopolysaccharidosis IVA (MPS IVA), also known as Morquio A syndrome, is a rare autosomal recessive lysosomal storage disorder caused by mutations in the gene encoding for N-acetylgalactosamine-6-sulfate sulfatase (GALNS), the enzyme responsible for the catabolism of keratan sulfate (KS) and chondroitin-6-sulfate, which are glycosaminoglycans (GAGs) found principally in skeletal and cartilaginous tissue.[1] As a result of this enzymatic defect, reduced enzyme activity causes incompletely degraded GAGs to accumulate to toxic levels in lysosomes, producing widespread skeletal dysplasia, including short stature and various skeletal deformities.[1,2] Unlike other MPS disorders, the central nervous system appears unaffected, thus preserving normal intellect among patients with MPS IVA; however, neurological complications can occur secondary to skeletal manifestations.[7] Extra-skeletal systems adversely affected by MPS IVA include visual, auditory, respiratory, cardiovascular, and digestive systems.[8] Manifestations described in the patient group input received by CADTH Common Drug Review (CDR) on this submission included hernias, chronic ear infections, hearing impairment, corneal clouding, diarrhea, heart disease (e.g., valvular[1]), respiratory disease, and sleep apnea.

The natural history of MPS IVA is not well established, although an industry-sponsored, multinational, longitudinal registry study is ongoing (MOR-CAP).[9] Likewise, estimates of the incidence of MPS IVA vary by region, ranging from one in 76,000 live births in Northern Ireland to one in 640,000 live births in western Australia.[8] An incidence of one per 200,000 live births has been reported for British Columbia.[1] According to research carried out by the sponsor of this submission, the estimated incidence of MPS IVA in Canada is 0.38 to 0.5 per 100,000 live births; at present, fewer than 100 patients with MPS IVA are estimated to be living in Canada.[3] The presentation and clinical course of the disease is highly variable, with severe and rapidly progressing forms typically presenting before the age of one year, moderate forms between one and five years, and attenuated or milder disease often diagnosed after the age of 20 years.[4] With more than 275 genetic mutations in the GALNS enzyme identified to date,[2] MPS IVA has been characterized as a disease of high genotypic and phenotypic heterogeneity.[5] MPS IVA is a progressive disease, in which death typically occurs in the second or third decade of life in patients with severe disease; by comparison, patients with milder disease can survive into their seventies.[1] Cause of death is usually cardiorespiratory failure or spinal cord complications.[10]

The definitive diagnosis of MPS IVA is established by enzymatic assay for GALNS activity in peripheral blood leukocytes.[6] Enzymatic assay is preceded by urine testing for total urine GAG levels, which may be triggered by abnormalities noted on clinical exam and/or radiographic findings. Because KS levels vary with age, urine GAG levels alone are unreliable for diagnosing MPS IVA.[6] Patients with more severe disease are easier to identify by their clinical presentation, while diagnosis of less severe forms of the disease may be delayed.[2]

1.2 Standards of Therapy

In the absence of therapies specifically indicated for MPS IVA, the standard of care for the management of MPS IV has been palliative, using a combination of medical and surgical interventions for symptom management with the goal of improving or maintaining quality of life for as long as possible.[1,5] A multidisciplinary team is typically involved in the care of patients with MPS IVA, reflective of the multiple organ systems affected by the disease. The only published clinical practice guideline for the treatment of MPS IVA identified in the literature appears to be an expert consensus statement sponsored by the

manufacturer; it was found to lack a methodology for generating recommendations, and levels of evidence for each recommendation were not reported.[11]

Widespread skeletal dysplasia is the hallmark of MPS IVA,[1,2] with frequent orthopaedic surgical interventions required to correct bone deformities.[2] Surgery is an inherently risky intervention in MPS IVA patients because they can have complex airway management needs arising from cervical instability and reduced respiratory function.[1] According to the clinical expert consulted by CDR, adjunctive pharmacotherapies used for symptom control include analgesics and bronchodilators; some patients may also require chronic medications to manage comorbidities, such as hypertension. Episodic courses of antibiotics may be required to treat acute respiratory infections, to which MPS IVA patients are particularly susceptible.[8]

1.3 Drug

Elosulfase alfa (ESA) is a recombinant formulation of human GALNS — the enzyme responsible for breaking down the glycosaminoglycans KS and chondroitin-6-sulfate — which is deficient in patients with MPS IVA. By replacing deficient GALNS, ESA is postulated to enhance the degradation and clearance of accumulated KS in patients with MPS IVA,[5] thereby having the potential, in theory, to modify the clinical course of disease. ESA is the first enzyme replacement therapy to be marketed in Canada for the treatment of MPS IVA. It is dosed at 2.0 mg/kg/week and is administered by IV infusion over four hours. ESA has a Health Canada indication as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of MPS IVA. The manufacturer is seeking reimbursement in accordance with this indication.

Indication under review
For long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis IVA (Morquio A syndrome, or MPS IVA)
Listing criteria requested by sponsor
As per indication

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ESA 2mg/kg IV once weekly as long-term enzyme replacement therapy in patients with MPS IVA.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies supporting the Health Canada indication provided in the manufacturer's submission to CDR as well as those meeting the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with a confirmed diagnosis of MPS IVA (Morquio A syndrome) Subgroups: • Age • Baseline 6MWT • Baseline ambulation: fully independent versus partial or full dependence on a mobility aid • Geographic region (i.e., North American patients)
Intervention	Elosulfase alfa 2 mg/kg IV once weekly
Comparators	Placebo Best supportive care

Outcomes	**Key efficacy outcomes:**
	• Survival
	• Disease progression
	  ○ Time to wheelchair dependency
	  ○ Time to requirement for respiratory assistance (e.g., ventilation support)
	  ○ Time to (or need for) surgeries (e.g., corrective orthopaedic)
	• Endurance
	  ○ 6MWD
	  ○ 3MSCT
	• Pulmonary function
	  ○ FVC, FEV_1, MVV
	Other efficacy outcomes:
	• Growth/development
	  ○ Weight/BMI
	  ○ Standing height (children)
	• Quality of life
	• Functional capacity
	• Urinary KS
	• Change in supportive therapies (e.g., pain medications, inhalers)
	Harms outcomes*:*
	AEs, SAEs, WDAEs, mortality

Study Design	Published and unpublished phase 3 RCTs

3MSCT = three-minute stair-climb test; 6MWD = six-minute walk distance; 6MWT = six-minute walk test; AE = adverse event; BMI = body mass index; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IV = intravenous; KS = keratan sulfate; MPS IVA = Morquio A syndrome; MVV = maximum voluntary ventilation; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event; y = years.

2.3 Supplemental Issues

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was elosulfase alfa (Vimizim).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on September 15, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on January 21, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessments, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, and databases. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

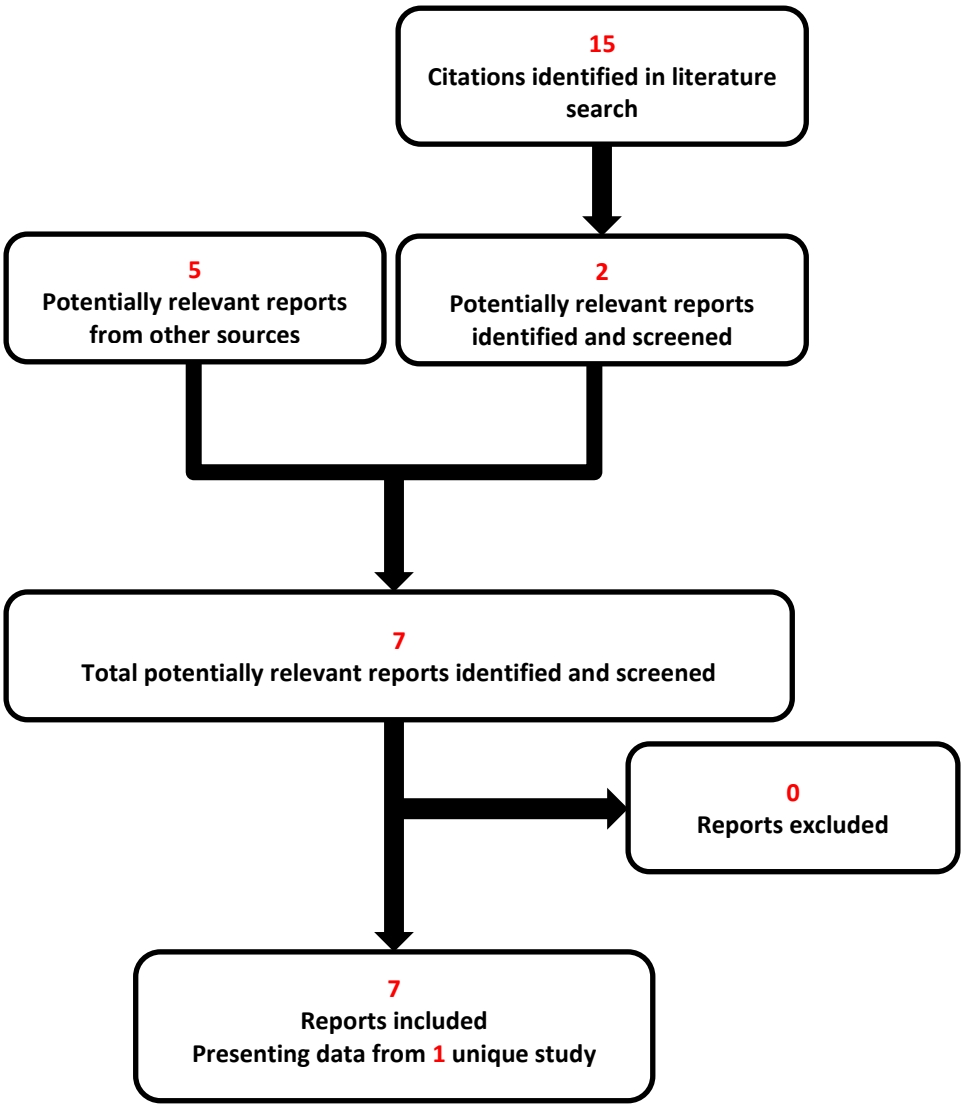


TABLE 3: DETAILS OF INCLUDED STUDIES

		MOR-004
DESIGNS & POPULATIONS	**Study Design**	• 24-week, multinational, DB, placebo-controlled parallel-arm (1:1:1) RCT • Randomization stratified by age and screening 6MWT
	Locations	33 study centres in 17 countries: Canada, USA, western Europe, South America, Asia
	Randomized (N)	177
	Inclusion Criteria	Patients ≥ 5 years old; documented clinical diagnosis of MPS IVA; mean screening 6MWT of ≥ 30 m and ≤ 325 m
	Exclusion Criteria	Previous hematopoietic SCT; previous treatment with ESA; known hypersensitivity to any component of ESA; major surgery ≤ 3 months before study entry or planned major surgery during the 24-week study treatment period; use of any investigational product or medical device ≤ 30 days before screening, or anticipated requirement for any investigational drug before completion of all scheduled study assessments; concurrent disease or condition (e.g., symptomatic cervical spine instability, clinically significant spinal cord compression, severe cardiac disease) that would interfere with study participation or safety.
DRUGS	**Intervention**	ESA 2.0 mg/kg by IV infusion either once weekly or once every other week[a]
	Comparator(s)	Matching placebo
DURATION	Run-in	Not applicable
	Double-blind	24 weeks
	Follow-up	OLE: MOR-005
OUTCOMES	**Primary End Point**	6MWT: change from baseline to week 24
	Other End Points	**Secondary:** 3MSCT: change from baseline to week 24; urine KS (normalized to creatinine): percentage change from baseline to week 24 **Supportive:** Composite (6MWT, 3MSCT, MVV): change from baseline to week 24; MVV : percentage change from baseline to week 24 **Tertiary:** PFTs; MPS HAQ; biomarkers for inflammation and for bone and cartilage metabolism; anthropometry (i.e., standing height, length, sitting height, weight); radiographs; audiometry examinations; echocardiogram; corneal clouding examinations
NOTES	**Publications**	Hendriksz et al. (2014)[10]

3MSCT = three-minute stair-climb test; 6MWT = six-minute walk test; DB = double-blind; ESA = elosulfase alfa; IV = intravenous; KS = keratin sulfate; MPS = mucopolysaccharidosis; MPS HAQ = MPS Health Assessment Questionnaire; MPS IVA = mucopolysaccharidosis IVA (Morquio A syndrome); MVV = maximum voluntary ventilation; OLE = open-label extension; PFT = pulmonary function test; RCT = randomized controlled trial; SCT = stem cell transplant.
[a] Only the once-weekly regimen was reviewed, as this is the Health Canada–approved dosing.
Note: Six additional reports were included.[3,12-16]
Source: MOR-004 Clinical Study Report.[12]

3.2 Included Studies

3.2.1 Description of studies

MOR-004 was a 24-week, multi-centre, multinational (17-country), three-arm, double-blind, randomized (1:1:1), placebo-controlled trial of 177 patients with MPS IVA, with randomization stratified by age and screening 6MWT. The majority (68.2%) of the 33 participating clinical centres were located in Europe (41.5%) and North America (26.7%). The primary objective of the trial was to test the efficacy and safety of two regimens of ESA compared with placebo in patients with a clinical diagnosis of MPS IVA (Morquio A syndrome). Because only the weekly (not the every-other-week) infusion regimen was approved by Health Canada, only data from the weekly regimen will be compared against placebo in this review.

3.2.2 Populations

a) Inclusion and exclusion criteria

MOR-004 enrolled patients with a clinical diagnosis of MPS IVA who were at least five years of age, did not have a history of surgical intervention in the three months preceding enrolment, and were not expected to require surgical intervention during the 24-week treatment phase of the trial. At screening, patients had to be able to walk a distance between ≥ 30 m and ≤ 325 m on the 6MWT for participation in the trial. Likewise, patients with concurrent disease or morbidity, such as symptomatic cervical spine instability, clinically significant spinal cord compression, or severe cardiac disease — which, in the judgment of the investigator, could interfere with participation or safety — were excluded. The clinical expert consulted by CDR indicated that the MOR-004 trial consisted primarily of patients with mild to moderate MPS IVA.

b) Baseline characteristics

Baseline characteristics (Table 4) were generally well balanced between the once-weekly ESA and placebo groups. The mean age of diagnosis of MPS IVA was 6.5 years; patients assigned to the placebo group had been living with the diagnosis almost two years longer, on average, than those in the ESA group (8.7 years versus 6.5 years). Patients enrolled in MOR-004 were almost evenly split in terms of gender, with females accounting for 55% of the total. Caucasian patients comprised 68% of the trial population, but there were fewer Caucasian patients in the ESA group than in the placebo group (62.1% versus 74.6%). Likewise, there were more Asian patients assigned to the ESA group compared with the placebo group (24.1% versus 18.6%). The overall mean age of patients was 14 years; a slight imbalance between groups was noted in the proportion of patients aged 19 years or older, in that there were fewer such patients in the ESA group compared with the placebo group (17.2% versus 23.7%). Mean standing height was comparable between groups at around 103.4 cm; by comparison, median z-scores between groups suggested that patients in the ESA group were slightly shorter for their age group than those in the placebo group (–6.5 versus –5.6). Overall, a majority (94%) of patients fell below the third percentile for height.

Wheelchair use was self-reported through a functional assessment questionnaire (i.e., MPS Health Assessment Questionnaire [HAQ]). At baseline, more patients in the ESA group reported using a wheelchair than did those in the placebo group (51.7% versus 37.3%), likely reflecting more severe or advanced disease among patients in the ESA group. An additional ~30% of patients reported using walking aids in each group. Mean 6MWT was similar between groups at baseline, at about 208 m; just over 60% of patients had a baseline 6MWT > 200 m, and about 17% of patients required the use of a walking aid to perform the 6MWT. For patients physically unable to perform the tests, a score of 0 was assigned. [redacted]

[redacted] Mean pulmonary function, urine KS, and three-minute stair-climb test (3MSCT) results were numerically similar between groups.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	ESA Once Weekly (n = 58)	Placebo (n = 59)
Age (years)		
Mean (SD)	13.1 (8.1)	15.0 (11.3)
Median (range)	11.1 (5 to 42)	11.9 (5 to 57)
Proportion 5 to 11 years, n (%)	32 (55.2)	30 (50.8)
Proportion 12 to 18 years, n (%)	16 (27.6)	15 (25.4)
Proportion ≥ 19 years, n (%)	10 (17.2)	14 (23.7)
Sex, n (%)		
Female	32 (55.2)	32 (54.2)
Race, n (%)		
Caucasian	36 (62.1)	44 (74.6)
Black or African-American	2 (3.4)	0
Asian	14 (24.1)	11 (18.6)
Other	6 (10.3)	4 (6.8)
Region, n (%)		
North America	15 (25.9)	16 (27.1)
Europe	25 (43.1)	27 (45.8)
Other	18 (31.0)	16 (27.1)
MPS IVA Diagnosis		
Time since diagnosis, mean (SD) years	6.5 (6.3)	8.7 (9.6)
Age at time of diagnosis, mean (SD) years	6.6 (7.1)	6.4 (6.4)
Mobility Aid Use[a]		
Wheelchair	30 (51.7)	22 (37.3)
Walking aid[c]	17 (29.3)	18 (30.5)
Weight (kg)		
Mean (SD)	22.9 (10.5)[d]	25.4 (11.5)
Median (range)	19.1 (12.0 to 68.5)	23.0 (12.6 to 67.3)
Height (cm)		
Standing, mean (SD)	101.3 (13.1)	105.5 (16.8)
Height Z-Score		
Mean (SD)	–6.4 (2.6)	–6.0 (2.8)
Median (range)	–6.5 (–11.0 to –2.1)	–5.6 (–11.4 to –1.4)
Height Percentile		
< 3rd percentile	56 (96.6)	54 (91.5)
≥ 3rd to < 10th percentile	0	4 (6.8)
≥ 10th percentile	0	0
Body Mass Index (kg/m^2)		
Mean (SD)	NR	NR

Characteristic	ESA Once Weekly (n = 58)	Placebo (n = 59)
Pulmonary Function		
FEV_1 (L)	0.8 (0.4)	1.0 (0.7)
FVC (L)	0.9 (0.5)	1.2 (0.9)
MVV	NR	NR
Normalized Urine KS[e] (mcg/mg)		
Mean (SD)	26.9 (14.1)	25.7 (15.1)
6MWT (m)		
Mean (SD)	203.9 (76.3)	211.9 (69.9)
Median (range)	216.5 (42 to 322)	228.9 (36 to 312)
Proportion ≤ 200 m, n (%)	23 (39.7)	23 (39.0)
Proportion > 200 m, n (%)	35 (60.3)	36 (61.0)
Any walking aids used,[h] n (%):	9 (15.5)	11 (18.6)
Crutches	1 (1.7)	4 (6.8)
Walker/walking frame	7 (12.1)	6 (10.2)
Cane/walking stick	1 (1.7)	1 (1.7)
3MSCT (stairs/minute)		
Mean (SD)	29.6 (16.4)	30.0 (14.1)
Median (range)		
Relevant Medical History, ≥ 1 Reported Finding		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3MSCT = three-minute stair-climb test; 6MWT = six-minute walk test; ESA = elosulfase alfa; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; KS = keratin sulfate; MPS IVA = mucopolysaccharidosis IVA (Morquio A syndrome); MVV = maximum voluntary ventilation; NR = not reported; SD = standard deviation.

[a] From MPS Health Assessment Questionnaire for patients with complete data.

[b] ESA n = 57, placebo n =57.

[c] ESA n = 57, placebo n = 56.

[d] n = 58.

[e] n = 56.

[f] n = 55.

[g] Normalized urine KS is calculated as urine KS divided by urine creatinine.

[h] Walking aids used in 6MWT include crutches, walker or walking frame, and cane or walking stick.

Source: MOR-004 Clinical Study Report.[12]

3.2.3 Interventions

Patients were assigned 1:1:1 to ESA 2.0 mg/kg given by IV infusion either weekly or every other week, or matching placebo for a total of 24 weeks. To maintain the blind, patients assigned to the alternate-week ESA regimen were infused with placebo during the intervening weeks when no active treatment was scheduled. Patients assigned to the placebo group received weekly infusions of placebo solution. The placebo solution was identical to ESA in appearance and consistency and contained the same excipients. Supportive therapies (e.g., analgesics), with the exception of investigational products, were permitted

during the trial. As stated previously, the CDR review specifically focused on the Health Canada–approved weekly ESA regimen compared with placebo.

Investigators were permitted to adjust the rate of infusion (i.e., pause or slow the rate), or discontinue it altogether in the event a patient experienced an infusion-associated reaction. If these measures were insufficient, additional medical intervention (i.e., IV antihistamines, steroids, fluids, or oxygen) was instituted at the investigator's discretion.

3.2.4 Outcomes

Endurance was assessed by the 6MWT and 3MSCT during MOR-004. The primary efficacy outcome in MOR-004 was the change from baseline in 6MWT after 24 weeks. This supervised, submaximal exercise test evaluates the total distance a patient can walk in six minutes over a standard, flat, 30-metre surface. Although there are no studies validating the use of the 6MWT in MPS diseases, regulatory authorities considered the 6MWT to be an acceptable surrogate in MPS IVA (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).[17] In addition to the 6MWT, the 3MSCT was a secondary efficacy outcome also designed to assess endurance. The original version of the 3MSCT evaluates the number of stairs climbed in the space of three minutes. However, because some patients were able to climb to the top of the staircase in less than three minutes, the test was subsequently modified to reflect the number of stairs climbed per minute over three minutes (this is the version employed in MOR-004). Despite the lack of validation studies for the 6MWT and 3MSCT in MPS IVA patients, these outcomes were considered appropriate markers of endurance for this population by the clinical expert consulted by CDR. No published minimal clinically important differences (MCIDs) for either the 6MWT or 3MSCT in MPS diseases were identified.

Urine KS, another secondary outcome in the trial, is a biomarker thought to be a surrogate of disease activity in MPS IVA. There are no published MCIDs for urine KS in MPS diseases.

The MPS HAQ, a disease-specific questionnaire that measures functional capacity or performance, consists of 52 questions distributed over three domains — self-care (27 items), mobility (12 items), and caregiver assistance (13 items) — the items within which are scored on a 10-point scale (0 = not difficult at all; 10 = extremely difficult) except for two questions in the mobility domain about wheelchair and walking aid use, which were scored separately in the trial.[12,18] The higher the scores recorded, the greater the degree of disability. As it was originally developed for use in MPS I disease, there has been some concern that this questionnaire may lack measurement sensitivity (i.e., the ability to detect changes) in MPS IV disease.[5] There are no published MCIDs for the MPS HAQ.

Pulmonary function tests (Table 5) were examined as a tertiary outcome in MOR-004, but there are no studies validating these tests as a measure of disease severity or progression in MPS IVA patients, and no published MCIDs in MPS disease were identified (APPENDIX 5: VALIDITY OF OUTCOME MEASURES). Table 5 presents a comparison of the outcomes studied in MOR-004 with those identified in the review protocol.

TABLE 5: EFFICACY AND SAFETY OUTCOMES IN MOR-004 VERSUS CDR SYSTEMATIC REVIEW PROTOCOL

MOR-004[12]	CDR Systematic Review Protocol
EFFICACY	
Primary:	**Key:**
• 6MWT: Change from baseline after 24 weeks	• Survival
	• Disease progression (i.e., time to: wheelchair dependency, requiring respiratory assistance, requiring corrective orthopaedic surgery)
	• Endurance (i.e., 6MWT, 3MSCT)
	• Pulmonary function (i.e., time to decline in FVC, FEV_1, MVV)
Secondary:	**Other:**

• Change from baseline after 24 weeks in:
  ○ 3MSCT
  ○ Urine KS
	• Growth and development
	  ○ Weight/BMI
	  ○ Standing height
	• Quality of life
	• Urinary KS
	• Change in supportive therapies

Tertiary:	
• Pharmacokinetics • Respiratory function tests (MVV, FVC, FEV_1, FIVC) • MPS HAQ • Biomarkers (inflammation, bone and cartilage metabolism) • Anthropometry • Radiographs • Audiometry examinations • Echocardiograms • Corneal clouding	
Safety	
• AEs • Standard clinical laboratory tests • Pregnancy tests • Vital signs • ECGs • Routine PE (including standard NE) • Concomitant medications	• AEs • SAEs • WDAEs • Mortality
• Immunogenicity tests	
• Demographic data	
• Medical history	
• Other lab assessments (in patients with SAE)	

3MSCT = three-minute stair-climb test; 6MWT = six-minute walk test; AE = adverse event; BMI = body mass index; CDR = CADTH Common Drug Review; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FIVC = forced inspiratory vital capacity; FVC = forced vital capacity; KS = keratan sulfate; MPS HAQ = mucopolysaccharidosis health assessment questionnaire; MVV = maximum voluntary ventilation; NE = neurologic exam; PE = physical examination; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

3.2.5 Statistical analysis

MOR-004 was a 24-week randomized controlled trial (RCT) designed to test the superiority of ESA compared with matching placebo on the primary efficacy outcome of the mean change in 6MWT from baseline to week 24. 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 intention-to-treat (ITT) or safety analyses would be required to detect a mean difference between ESA (either the weekly or alternate-weekly ESA regimens) and placebo of 40 m. There was no mention of invalidity rate considerations in the calculation. Outcomes were analyzed using a modified intention-to-treat (mITT) principle, which included all randomized patients who received at least one dose of study drug. There was no formal interim analysis planned.

a) Primary efficacy outcome — 6MWT

Two 6MWTs were conducted for each visit on separate days and then averaged. For patients physically unable to perform the tests, a score of 0 was assigned. The primary analysis used analysis of covariance (ANCOVA) for modelling the change from baseline to week 24, with treatment, age, and baseline 6MWT as factors; repeated measures ANCOVA was also performed as a supportive analysis. The Hochberg method was used to adjust for multiple testing across the three arms to maintain an overall Type I error rate of 0.05. No formal statistical testing to evaluate the normality of the data was conducted. Instead, the normality of the data, along with the presence of outliers and the dependence of 6MWT variability on treatment, were explored using graphical techniques. Several sensitivity tests were conducted, including an evaluation of the effect of duplicate 6MWT testing (i.e., analysis of the two test results individually or of the better of the two results, instead of the average of the two results), imputation method, distributional assumptions, and incorporation of a term in the ANCOVA model to model the interaction between treatment and baseline 6MWT strata (≤ 200 m and > 200 m).

Pre-specified subgroup analyses were conducted on the primary efficacy outcome to examine possible treatment-by-subgroup interactions; these subgroups included screening 6MWT categories (≤ 200 m, > 200 m), age (five to 11 years, 12 to 18 years, ≥ 19 years), sex, race (Caucasian versus non-Caucasian), and geographic region (North America, Europe, Other).

b) Secondary efficacy outcomes — three-minute stair-climb test, urine keratan sulfate

Similar to the 6MWT, two 3MSCTs were conducted for each visit on separate days and then averaged. For patients physically unable to perform the tests, a score of 0 was assigned. The primary analysis of the change from baseline to week 24 in 3MSCT and urine KS likewise used an ANCOVA model with similar parameters as for the 6MWT, except for the inclusion of baseline 3MSCT and urine KS as factors in their respective analyses. As with the primary efficacy analysis, repeated measures ANCOVA was also performed as a supportive analysis. To adjust for multiplicity in the secondary efficacy outcomes analysis, a step-down testing procedure was used, wherein the results of the 3MSCT were tested first, followed by urine KS; results of the latter could only be declared statistically significant if those of the former were statistically significant. As with the primary efficacy analysis, the Hochberg method was used to adjust for multiple testing to maintain an overall Type I error rate of 0.05. Similar sensitivity analyses as were employed to test results from the primary efficacy analysis were employed to test the findings from the secondary efficacy analyses.

c) Additional supportive efficacy outcomes — maximum voluntary ventilation, composite outcome

Maximum voluntary ventilation (MVV) and a composite consisting of the 6MWT, 3MSCT, and MVV were also analyzed using similar ANCOVA analyses and sensitivity testing as used in the primary and secondary efficacy analyses. The results of the composite are not reported in this review.

d) Tertiary (exploratory) efficacy outcomes

Tertiary efficacy outcomes — which included pulmonary function tests (PFTs) (e.g., forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1] MVV), quality of life (MPS HAQ), and anthropometric (e.g., weight, standing height) outcomes of interest to the systematic review protocol — were analyzed descriptively; mean differences, odds ratios, or relative risk ratios with 95% confidence intervals (CIs) were presented.

e) Minimal clinically important differences — six-minute walk test, three-minute stair-climb test, maximum voluntary ventilation, and composite outcome

In order to conduct responder analyses on what the manufacturer considered key efficacy outcomes (i.e., 6MWT, 3MSCT, MVV, and composite outcome) in the trial, an attempt was made to define a pre-specified MCID for each of the outcomes of interest using a combination of literature review and a Delphi consensus panel prior to the unblinding of the trial. Unfortunately, these efforts proved unsuccessful, such that the responder analyses that were ultimately carried out were conducted in a post hoc manner and thus should be considered exploratory.

f) Missing data

Multiple imputations (not further elaborated in the available documents) were used in the primary analysis for 6MWT, 3MSCT, urine KS, and PFTs when data were not available for a visit week for reasons other than death or physical disability.

g) Safety

The manufacturer conducted safety analyses on the incidence, severity grade, and relationship to study drug of all treatment-emergent adverse events (AEs) reported during the trial. Changes from baseline in clinical laboratory results and vital signs were also included in the safety reporting.

h) Analysis populations

The primary analysis set for performing efficacy analyses in MOR-004 was the ITT set, defined by the manufacturer as all randomized patients who received at least one dose of treatment. It should be noted that a true ITT set consists of all randomized patients regardless of treatment received; thus, the ITT set in MOR-004 must be considered a modified ITT set. The safety analysis set was defined in the same way as the ITT set.

3.3 Patient Disposition

In MOR-004, a total of 177 patients were randomized (1:1:1). One patient in the placebo group was excluded from all analyses due to non-confirmation of MPS IVA diagnosis; the patient did not receive a single dose of study medication. This excluded patient was the reason for the modified ITT set. In the full trial (i.e., three arms), the (modified) ITT set (n = 176) consisted of 58 patients randomized to weekly ESA, 59 to alternate-weekly ESA, and 59 to placebo. As stated previously, this review is limited to assessing the Health Canada-approved ESA weekly regimen versus placebo. One patient in the ESA weekly arm discontinued prematurely from the trial, but not from the drug; aside from the placebo patient who was excluded post-randomization for non-confirmation of MPS IVA diagnosis, no patients discontinued prematurely from the placebo arm. Follow-up data were complete for 116 of 117 (99.1%) patients (Table 6).

TABLE 6: PATIENT DISPOSITION

	MOR-004	
	ESA	**PB**
Screened, N	204	
Randomized, N (%)	58	60[a]
Discontinued, N (%)	1[b]	0
ITT, N	58 (100)	59 (98.3)
Safety, N	58 (100)	59 (100)

ESA = elosulfase alfa 2.0 mg/kg IV once weekly; ITT = intention-to-treat; MPS IVA = mucopolysaccharidosis IVA (Morquio A syndrome); PB = placebo.
[a] One patient was excluded prior to receipt of any study drug because of unconfirmed MPS IVA diagnosis.
[b] Discontinued study but not study drug.
Source: MOR-004 Clinical Study Report.[12]

3.4 Exposure to Study Treatments

The mean (standard deviation; SD) total duration of treatment was 23.6 (3.0) weeks for the ESA group compared with 24.0 (0.2) weeks for the placebo group. The mean (SD) total dose per patient was 46.2 (6.2) mg/kg for ESA compared with a nominal mean dose of 47.6 (0.8) mg/kg for the placebo group.

Compliance with the study drug was assessed as the total number of infusions administered and the number of incomplete infusions. Dosing compliance was defined as the proportion of total actual dose (mg/kg) divided by the total planned dose (mg/kg). (Planned infusions included infusions scheduled until the patient's study drug termination.) The mean (SD) total number of infusions administered was 23.2 (3.1) in the ESA group compared with 23.8 (0.4) in the placebo group, while the mean (SD) number of incomplete infusions was 0.2 (0.5) in the ESA group compared with 0.1 (0.3) in the placebo group. Mean (SD) dosing compliance was 96.8% (9.7%) in the ESA group and 99.2% (1.8%) in the placebo group. The number of missed infusions was 25 (1.8%) in the ESA group and 9 (0.6%) in the placebo group, while the number of patients with missed infusions was 18 (31.0%) in the ESA group and 8 (13.6%) in the placebo group. Infusions were interrupted or discontinued because of an adverse event requiring medical intervention in 13 (22.4%) patients in the ESA group, but in none in the placebo group (Table 12).

3.5 Critical Appraisal

3.5.1 Internal validity

- Overall, the trial was executed with appropriate allocation concealment and randomization. An interactive voice response system was used for treatment allocation. There is some doubt, however, about whether blinding may have been compromised to some degree due to the higher rate of infusion-associated reactions requiring medical intervention in the ESA arm.
- A few imbalances in baseline characteristics were noted between treatment arms (Table 4), which could affect the findings. Patients assigned to the placebo group had been living with a diagnosis of MPS IVA for almost two years longer, on average, than those in the ESA group (8.7 years versus 6.5 years). An earlier diagnosis could reflect the presence of more severe disease, which may be more likely to be identified sooner than milder disease phenotypes, which may not bear classic disease stigmata; however, it is unclear whether disease severity modifies response to therapy. Although some racial imbalances were noted, based on current knowledge, race would not be expected to modify response to therapy. There were fewer patients aged 19 years or older in the ESA group compared with the placebo group (17.2% versus 23.7%); however, it is unclear whether age modifies response to therapy, and age was included as a covariate in the analysis of 6MWT and

other outcomes. The majority (94%) of trial patients fell below the third percentile for height, with patients in the ESA group being slightly shorter for their age group than those in the placebo group (z-score of –6.5 versus –5.6). Though short stature has been considered a marker for more severe disease,[6] as mentioned previously, it is unclear whether disease severity modifies response to therapy.

- Follow-up data were complete for 99.1% (116/117) through the double-blind phase of the trial. Only one patient in the placebo group was excluded from all analyses due to non-confirmation of MPS IVA diagnosis; the patient did not receive a single dose of study medication. The ITT analysis set therefore did not include the randomized set, and so actually represents a modified ITT analysis set, as this individual's data were excluded. However, it is unlikely that this would have greatly affected the results of the study.
- The 6MWT, an intermediate end point, was the primary efficacy outcome in MOR-004; however, no validation studies or studies to determine an MCID have been conducted in the MPS diseases. Much of the evidence regarding the validity of this outcome is from cardiopulmonary conditions, whereas the pathophysiology of MPS IVA is characterized by musculoskeletal abnormalities. This further calls into question the validity of 6MWT in MPS IVA. Other issues include a documented learning effect, and potential limitations that are specific to the use of 6MWT in children (APPENDIX 5: VALIDITY OF OUTCOME MEASURES), although the potential for bias from these aspects may be low, as all treatment arms should be equally affected, on average, in an RCT. Despite these limitations, the FDA accepted the use of 6MWT as an outcome for trials in patients with MPS IVA. Other issues related to the 6MWT outcome were as follows:
  - A subgroup analysis based on baseline 6MWT distance was performed dichotomizing patients into either 6MWT ≤ 200 m or > 200 m. The rationale for the 200 m threshold was not provided, however; therefore, it is unclear how this cut-off point was derived and whether it was done so in an *a priori* or *a posteriori* manner.
  - The inability to escalate or de-escalate mobility aids according to clinical improvement or deterioration, respectively, over the course of study MOR-004 could have been a source of bias in the trial. While bias could occur in either group (in opposite directions), it is more likely that the net effect of that bias would be to favour treatment with ESA as a consequence of an inability to support deteriorating physical mobility in the placebo group.
- Urine KS is a biomarker that was studied as a secondary outcome in the trial; however, its validity as a surrogate of disease activity in MPS IVA is unknown.
- The 3MSCT was a secondary efficacy outcome in MOR-004. Due to some patients being able to climb to the top of the staircase in less than three minutes, the original definition of the 3MSCT was modified from assessing the number of steps climbed in three minutes to the number of steps climbed per minute during a three-minute interval. It is uncertain whether this change in definition was validated. Furthermore, no information was provided about staircase standardization across clinical sites, such as rise and run of the steps, or height and consistency in the use of railings.
- The MPS HAQ, a questionnaire that measures functional capacity, was a tertiary (exploratory) efficacy outcome in MOR-004, and the clinical expert confirmed its use in MPS IVA in clinical practice. The questionnaire was originally developed for use in MPS I; however, there are notable differences in pathology between the two MPS disease subtypes. In particular, MPS IVA is characterized by joint laxity, while MPS I is distinguished by joint stiffness.[5] In addition, MPS IVA is considered a more multi-faceted disease than MPS I.[5] Therefore, the measurement properties of MPS HAQ in MPS IVA are uncertain. In fact, it has been described in the literature as possibly lacking measurement sensitivity in MPS IVA.[5]

3.5.2 External validity

- A trial duration of 24 weeks was selected for MOR-004 to be able to detect changes in endurance surrogates (6MWT, 3MSCT) based on findings from an earlier-phase trial in the clinical development program and also on the design of other phase 3 trials of enzyme replacement therapy. The trial duration also reflected ethical considerations associated with delaying surgery balanced against the long post-operative convalescence period typical of MPS IVA patients; 24 weeks was thought to reflect the maximum length of time that surgery could reasonably be delayed without adverse consequence to patients. The trial duration may have been adequate to assess changes in intermediate outcomes such as the 6MWT, but it was considered too short to assess durability of effect[17] and clinical end points, such as the need for surgery or mobility aids (e.g., wheelchair). The trial was also likely too short to evaluate changes in height or linear growth.
- Patients were enrolled in the trial if their screening 6MWT was between ≥ 30 m and ≤ 325 m; therefore, mild and severe MPS IVA cases would have been screened out. This range was selected because it was thought that patients meeting this standard would have the greatest chance of demonstrating improvement (in 6MWT) with ESA. Likewise, patients who could not delay surgical intervention for six months (i.e., the treatment phase of MOR-004) would not have been enrolled into MOR-004, likely screening out severe MPS IVA cases. These selection criteria potentially limit the generalizability of findings to intermediate or moderate MPS IVA cases.
- As described above, the inability of patients to escalate or de-escalate mobility aids may have introduced bias in the 6MWT outcome in favour of ESA. This aspect of the trial also represents a limitation with respect to external validity, as it does not reflect the approach used to monitor or treat patients in clinical practice.
- The degree of dependency on a wheelchair — a key marker of disease progression, according to the clinical expert consulted by CDR — was assessed in some detail in the MPS HAQ questionnaire (i.e., frequency of use categorized as less than 50%, about 50%, more than 50%, or 100% of the time for ambulation),[18] but separately from the questionnaire's mobility domain score calculation. The proportion of patients requiring the use of a wheelchair during the trial was presented descriptively, but the extent of wheelchair dependence (i.e., frequency of use for ambulation) was not described, hampering an assessment of the generalizability of the trial population — particularly on the level of physical functioning — to MPS IVA patients treated in clinical practice. The lack of information presented about the extent of wheelchair dependence also somewhat complicates the interpretation of the 6MWT results, in that wheelchair use data reported at baseline seem to conflict with those reported specifically for the 6MWT. The 6MWT is a test designed to be performed without the use of a wheelchair, such that patients who were fully wheelchair-bound (i.e., unable to physically perform the 6MWT) were assigned a score of 0.
- The overall mean age of patients in the trial was 14 years (range: five to 57 years), with the majority (~80%) of patients being under 19 years. Thus, the trial's findings would appear most generalizable to the adolescent and preadolescent populations, which is consistent with the age group of patients most frequently encountered in clinical practice in Canada, according to the clinical expert consulted by CDR.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 2). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Survival

Survival was not studied as an efficacy outcome in MOR-004. However, no deaths were reported during the trial.

3.6.2 Disease progression

Disease progression — as defined in the CDR systematic review protocol as the time to a) wheelchair dependency; b) requiring respiratory assistance; or c) requiring corrective orthopaedic surgery — was not studied as an efficacy outcome in MOR-004. However, descriptive data on wheelchair use at baseline and at week 24 were presented and are described in Figure 2 in APPENDIX 4: DETAILED OUTCOME DATA. At baseline, wheelchair use was reported in 51.7% (30/58) of patients in the ESA group and 37.3% (22/59) in the placebo group. At week 24, the total number of patients reporting the use of a wheelchair did not change in the ESA group, but increased in the placebo group to 27 patients. Data were missing for three patients.

3.6.3 Endurance

a) Six-minute walk test

The change in 6MWT from baseline to week 24 was the trial's primary efficacy outcome. After 24 weeks, a statistically significant increase in the 6MWT was observed from baseline favouring ESA over placebo (adjusted least squares [LS] mean difference: 22.5 m; 95% CI, 4.0 m to 40.9 m) (Table 7).

The manufacturer conducted several pre-specified subgroup analyses of the primary outcome, which coincided with the subgroups of interest identified in the systematic review protocol; these included age (five to 11 years; 12 to 18 years; ≥ 19 years), baseline 6MWT (< 200 m; ≥ 200 m), and geographic region (Europe; North America; other). Baseline ambulation was also identified as a subgroup of interest in the systematic review protocol, but was not analyzed in MOR-004. In the subgroup of patients aged 12 to 18 years (n = 31), a statistically significant increase in the 6MWT was observed from baseline favouring ESA once-weekly treatment over placebo (adjusted LS mean difference: 48.2 m; 95% CI, 12.4 m to 84.0 m) (Table 9), while the results for the younger and older subgroups were not statistically significant. In the subgroup of patients with a baseline 6MWT ≤ 200 m (n = 46), a statistically significant increase in the 6MWT was observed from baseline favouring ESA treatment (adjusted LS mean difference: 40.4 m; 95% CI, 11.0 m to 69.8 m) (Table 9), but not in patients with a baseline 6MWT > 200 m. In the subgroup of patients drawn from North America (n = 31), a statistically significant increase in the 6MWT was observed from baseline favouring ESA treatment (adjusted LS mean difference: 43.4 m; 95% CI, 7.5 m to 79.3 m) (Table 9). However, tests of interaction were not statistically significant for any of these subgroup analyses. Given the small cell sizes for the various subgroups and the consequent limitations in statistical power, the lack of statistically significant results in some comparisons cannot be interpreted to represent a lack of benefit from ESA.

b) Three-minute stair-climb test

The change in 3MSCT from baseline to week 24 was a secondary outcome in the trial. After 24 weeks, there was no statistically significant difference in the 3MSCT between the ESA once weekly and placebo groups (adjusted LS mean difference: 1.1 stairs/min; 95% CI, –2.1 stairs/min to 4.4 stairs/min) (Table 7).

3.6.4 Pulmonary function

Pulmonary function was assessed as a tertiary (exploratory) outcome in MOR-004, but was considered a key efficacy outcome in the review protocol — specifically, FVC, FEV_1, and MVV. For each of the three PFT outcomes, in which percentage change from baseline to week 24 was examined, there was no statistically significant difference observed between the ESA and placebo groups (Table 7).

3.6.5 Other efficacy outcomes

Other efficacy outcomes specified in the review protocol were changes in growth and development, as evidenced by changes in weight and standing height; quality of life; urine KS; and supportive therapies (e.g., medications). Of these outcomes, only urine KS, which was a secondary outcome in MOR-004, was compared between the ESA and placebo groups. Changes in weight, standing height, and quality of life — all of which were tertiary outcomes in MOR-004 — were analyzed descriptively, while changes in supportive therapies were not analyzed.

a) Standing height and weight

Within-group changes from baseline to week 24 were presented for each group for all patients and for patients who still had growth potential (i.e., males aged ≤ 18 years and females aged ≤ 15 years) for the outcomes of weight and standing height. Overall, changes in standing height were small but directionally supportive of growth in both groups; however, growth was not reflected in corresponding z-score changes. Likewise, for weight, gains were consistently noted in both groups (Table 10).

b) Quality of life

No data were available regarding health-related quality of life.

c) Functional capacity

Within-group changes from baseline to week 24 were also presented for changes in functional capacity, as measured by the MPS HAQ. For the three domains — self-care, mobility, and caregiver assistance — changes were small, but directionally supportive of an improvement in functioning in both groups (Table 11).

d) Urine keratan sulfate

The per cent change in urine KS from baseline to week 24 was a secondary outcome in the trial. After 24 weeks, a statistically significant decrease in urine KS was observed from baseline favouring ESA treatment (adjusted LS mean difference: –40.7%; 95% CI, –49.0% to –32.4%). While it is difficult to interpret the meaningfulness of absolute changes in urine KS, these data would be considered supportive of the efficacy of ESA according to the clinical expert consulted by CDR. However, according to the trial's statistical plan, which included step-down testing of secondary outcomes to adjust for multiplicity, any differences between treatments in urine KS could only be considered statistically significant if the findings from the 3MSCT were statistically significant. Since there was no significant difference between groups in the latter outcome, the apparent statistical significance of the urine KS result should be disregarded.

e) Supportive therapies

Change in supportive therapies was not studied as an efficacy outcome in MOR-004.

TABLE 7: KEY EFFICACY OUTCOMES

	MOR-004	
6MWT (m)	**ESA Once Weekly (n = 58)**	**Placebo (n = 59)**
N	57	59
Baseline, mean (SD)	203.9 (76.3)	211.9 (69.9)
Week 24 — change from baseline, mean (SD)	36.5 (58.5)	13.5 (50.6)
LS mean difference (95% CI)	22.5 (4.0 to 40.9)	
P value[a]	0.0174	
3MSCT (STAIRS/MIN)		
N	57	59
Baseline, mean (SD)	29.6 (16.4)	30.0 (14.1)
Week 24 — change from baseline, mean (SD)	4.8 (8.1)	3.6 (8.5)
LS mean difference (95% CI)	1.1 (–2.1 to 4.4)	
P value[a]	0.4935	
FVC (%)		
N	55	53
Baseline, mean (SD)	0.9 (0.5)	1.2 (0.9)
Week 24 — % change from baseline, mean (SD)	4.9 (12.0)	1.5 (14.2)
LS mean difference (95% CI)	3.3 (–3.1 to 9.6)	
P value[a]	0.3041	
FEV_1 (%)		
N	58	59
Baseline, mean (SD)	0.8 (0.4)	1.0 (0.7)
Week 24 — % change from baseline, mean (SD)	5.4 (11.5)	2.5 (16.8)
LS mean difference (95% CI)	1.8 (–5.5 to 9.2)	
P value[a]	0.6129	
MVV (%)		
N	49	50
Baseline, mean (SD)	28.3 (16.6)	34.8 (27.3)
Week 24 — % change from baseline, mean (SD)	10.8 (25.6)	2.4 (20.7)
LS mean difference (95% CI)	10.3 (–1.8 to 22.4)	
P value[a]	0.0943	

3MSCT = three-minute stair-climb test; 6MWT = six-minute walk test; CI = confidence interval; ESA = elosulfase alfa; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; KS = keratan sulfate; ITT = intention-to-treat; LS = least squares; MVV = maximum voluntary ventilation; m = metres; min = minute; SD = standard deviation.

[a] *P* value determined by t-test from ANCOVA model.

Note: ITT analysis set used for modelling LS mean difference; observed cases used for reporting group means. Baseline covariates adjusted in the model were age group (all presented outcomes); 6MWT category (all presented outcomes); continuous 3MSCT (for 3MSCT only); FVC (for FVC only); primary composite score, i.e., the average of component changes in normalized 6MWT, 3MSCT, and MVV from baseline measured at week 24 (for FEV_1 only); and MVV (for MVV only).

Source: MOR-004 Clinical Study Report.[12]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse events

The overall frequency of AEs was similar between the ESA and placebo groups (96.6% versus 96.6%). The most commonly occurring AEs in ESA-treated patients, which also appeared to occur at a higher frequency than in the placebo group, were vomiting (44.8% versus 35.6%), pyrexia (43.1% versus 28.8%), headache (41.4% versus 35.6%), nausea (31.0% versus 20.3%), abdominal pain (24.1% versus 8.5%), diarrhea (20.7% versus 11.9%), oropharyngeal pain (20.7% versus 11.9%), upper abdominal pain (15.5% versus 8.5%), otitis media (15.5% versus 6.8%), dizziness (12.1% versus 5.1%), dyspnea (12.1% versus 5.1%), gastroenteritis (12.1% versus 6.8%), and chills (10.3% versus 1.7%). According to the clinical expert consulted by CDR, many of these AEs would be considered infusion-associated reactions, and manageable in a clinic setting. However, in the absence of information regarding the timing of the reactions in relation to infusion, it is difficult to determine the extent to which they were truly infusion-related.

3.7.2 Serious adverse events

Serious adverse events were more common with ESA treatment than placebo (15.5% versus 3.4%), with infections and infestations classified as serious adverse events occurring in 8.6% of patients in the ESA group and none in the placebo group.

3.7.3 Withdrawals due to adverse events

There were no withdrawals due to AEs reported during the trial.

TABLE 8: HARMS

	MOR-004	
AEs	**ESA (n = 58)**	**Placebo (n = 59)**
Patients with ≥ 1 AEs, N (%)	56 (96.6)	57 (96.6)
Most common AEs (≥ 10%):		
Vomiting	26 (44.8)	21 (35.6)
Pyrexia	25 (43.1)	17 (28.8)
Headache	24 (41.4)	21 (35.6)
Nausea	18 (31.0)	12 (20.3)
Cough	16 (27.6)	21 (35.6)
Abdominal pain	14 (24.1)	5 (8.5)
Diarrhea	12 (20.7)	7 (11.9)
Oropharyngeal pain	12 (20.7)	7 (11.9)
Arthralgia	10 (17.2)	17 (28.8)
Nasopharyngitis	10 (17.2)	9 (15.3)
Upper respiratory tract infection	10 (17.2)	9 (15.3)
Abdominal pain upper	9 (15.5)	5 (8.5)
Fatigue	9 (15.5)	15 (25.4)
Otitis media	9 (15.5)	4 (6.8)

	MOR-004	
AEs	**ESA (n = 58)**	**Placebo (n = 59)**
Pain in extremity	9 (15.5)	9 (15.3)
Back pain	7 (12.1)	6 (10.2)
Dizziness	7 (12.1)	3 (5.1)
Dyspnea	7 (12.1)	3 (5.1)
Gastroenteritis	7 (12.1)	4 (6.8)
Chills	6 (10.3)	1 (1.7)
Oxygen saturation decreased	6 (10.3)	6 (10.2)
Rash	6 (10.3)	5 (8.5)
SAEs		
Patients with ≥ 1 SAEs, N (%)	9 (15.5)	2 (3.4)
Any SAEs:		
Pneumonia	2 (3.4)	0
Hypersensitivity	1 (1.7)	0
Infusion site pain	1 (1.7)	0
Lower respiratory tract infection	1 (1.7)	0
Otitis media	1 (1.7)	0
Urticaria	1 (1.7)	0
Viral upper respiratory tract infection	1 (1.7)	0
Vomiting	1 (1.7)	0
Anaphylactic reaction	0	0
Cervical cord compression	0	1 (1.7)
Deafness	0	1 (1.7)
Dengue fever	0	0
Suture removal	0	0
WDAEs		
WDAEs, N (%)	0	0

AE = adverse event; ESA = elosulfase alfa; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: MOR-004 Clinical Study Report.[12]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from one phase 3 (MOR-004) double-blind, randomized (1:1:1), placebo-controlled trial comprising 176 patients aged five years or older with a confirmed diagnosis of MPS IVA. Patients were randomly assigned to either a weekly or alternate-weekly regimen of ESA 2.0 mg/kg or matching placebo for 24 weeks. This systematic review considered only the weekly regimen of ESA, as this was the Health Canada–approved regimen.

4.2 Interpretation of Results

4.2.1 Efficacy

The primary efficacy outcome in MOR-004 was the change in the six-minute walk test (6MWT) — a marker of endurance — from baseline to 24 weeks. By comparison, the review protocol considered survival and time to disease progression to be key efficacy outcomes followed by markers of endurance (in which the 6MWT was included) and pulmonary function. Survival and time to disease progression, however, were not reported in MOR-004, nor was this trial long enough to capture these outcomes meaningfully. Patient input for this submission (APPENDIX 1: PATIENT INPUT SUMMARY) corroborated disease progression, specifically stabilizing or slowing the disease, as an important clinical outcome. In addition, reduced endurance coupled with the morbidity associated with bone and joint disease (e.g., pain) were cited as having the greatest impact on a patient's quality of life. Data for progression to wheelchair dependence, which was a key outcome in the submitted pharmacoeconomic model,[19] were presented only descriptively, and were largely uninformative.

A statistically significant increase in 6MWT was observed from baseline to week 24, favouring ESA (adjusted LS mean difference: 22.5 m; 95% CI, 4.0 m to 40.9 m). Pre-specified subgroup analyses that were performed and were of interest to the systematic review — age, baseline 6MWT, and geographic region — were directionally consistent and supportive of the primary analysis for an effect of ESA treatment, and there were no statistically significant treatment-by-subgroup interactions. In the absence of a defined MCID for the 6MWT in MPS diseases, the clinical meaningfulness of this change is uncertain. Further complicating the interpretation is uncertainty as to whether there is a correlation between improvement in 6MWT and improvement in outcomes of direct relevance to patients, namely pain, fatigue, physical functioning (e.g., ability to perform activities of daily living), quality of life, and need for mobility aids. Nevertheless, the FDA accepted the 6MWT as an intermediate outcome for MPS IVA trials,[17] and approval of ESA by this and other regulators implies that the observed improvement in 6MWT in MOR-004 was considered clinically relevant. However, the FDA did acknowledge that the 6MWT fell short in capturing information about pain and fatigue associated with the disease.[17]

Findings from the 3MSCT —another marker of endurance — as well as urine KS, key PFTs (i.e., FVC; FEV_1; MVV), anthropometry (i.e., standing height, weight), and functionality as measured by the MPS HAQ were all directionally supportive of an ESA treatment effect, but results were either not statistically significant or, in the case of tertiary outcomes, statistical comparisons were not performed.

From the patient input received for this submission (APPENDIX 1: PATIENT INPUT SUMMARY), reduced endurance, and pain from bone and joint disease (e.g., spine, hips, and knees) were identified as having a significant impact on quality of life. Patients expressed a desire to see disease progression stabilized or slowed, with treatment expected to improve mobility and thus increase quality of life, increase (vertical) growth, and reduce the risk of cervical cord compression. Patients also anticipated that improvements

from treatment would lead to fewer procedures and less time away from school or work. Unfortunately, except for limited and uncertain data on endurance from the 6MWT, these patient-important outcomes were largely unaddressed by the MOR-004 trial. While the MPS HAQ attempted to capture some quality-of-life data related to self-care, mobility, and caregiver assistance, these data were minimally informative owing to the lack of comparative statistics. Moreover, the MPS HAQ is an instrument originally developed for use in MPS I, an MPS disease subtype distinct from MPS IVA. Where MPS IVA is characterized by joint laxity, MPS I is distinguished by joint stiffness.[5] In addition, MPS IVA is considered a more multi-faceted disease than MPS I.[5] Thus, the measurement properties of MPS HAQ in MPS IVA are uncertain.

MPS IVA is a progressive disease affecting bone and connective tissue metabolism, which in its most severe form typically leads to death by the second or third decade of life.[1] Prior to the availability of ESA, there were no approved medications for the treatment of MPS IVA, so treatment was largely palliative. As an enzyme replacement therapy, there is some biologic plausibility that by restoring deficient GALNS enzyme activity, there may be a reduced need for downstream surgical interventions (particularly corrective orthopaedic surgeries) and potentially an increase in life expectancy. However, because hard clinical end points such as these were not studied in the trial, it remains unknown whether ESA represents a disease-modifying therapy.

The natural history of MPS IVA is not well established. With more than 275 mutations identified in the GALNS gene thus far,[2] MPS IVA is a disease distinguished by substantial genotypic and phenotypic heterogeneity,[5] and a highly variable clinical course. The MOR-004 study population seemed to represent a population composed primarily of patients with intermediate or moderate disease, based on the trial's baseline characteristics. The trial's selection criteria would have screened out more severe disease, particularly because of the restrictions placed on surgical interventions, and milder disease with the 6MWT ceiling of 325 m. It also seems probable that patients with milder disease (i.e., less disease burden, higher functionality) are likely underdiagnosed in the population, and thus would be under-represented in trials generally, as their disease phenotype would make them less easily identifiable as having MPS IVA.

As a disease affecting normal growth and development, particularly linear growth potential, it seems relevant to consider how the efficacy of ESA treatment might change depending on when the drug is initiated in relation to growth plate closure. That is, how much effect would the drug have if commenced after growth plate fusion, or once irreversible skeletal damage had occurred? Anthropometric outcomes, such as standing height, were investigated as tertiary outcomes in the trial, and so were only examined descriptively for changes occurring within groups. However, data were presented separately for patients still deemed to have linear growth potential (i.e., males aged ≤ 18 years and females ≤ 15 years) alongside data for all trial patients. Given the short trial duration of 24 weeks, the post hoc nature of these age groupings, and the lack of comparative statistics, it is difficult to draw conclusions about the changes observed. Likewise, the findings from the pre-specified subgroup analyses performed on age categories of five to 11 years, 12 to 18 years, and ≥ 19 years were inconclusive in terms of identifying possible signals of differential efficacy among the three age subgroups; although mean difference estimates were directionally supportive of ESA treatment (and thus, the findings from the primary analysis), only the 12-to-18-years subgroup analysis achieved statistical significance. The overall mean age of patients in the trial was 14 years, with ages ranging between five and 57 years; however, the majority (~80%) of patients were younger than 19 years of age. Thus, the findings would appear most generalizable to the adolescent and preadolescent populations,

which is consistent with the age group of patients treated in clinical practice in Canada, according to the clinical expert consulted by CDR.

Upon completion of MOR-004, patients were invited to participate in MOR-005, an open-label extension study (APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY) designed to run until either 240 weeks of treatment were completed or the study was terminated. Of the 175 patients eligible to enroll in MOR-005, 173 (98.9%) chose to enrol, including 56 (98.2%) patients originally assigned to weekly ESA treatment. During Part I of MOR-005, patients who received ESA treatment during MOR-004 continued to receive their same regimen (i.e., weekly or alternate-weekly dosing), while patients who received placebo during MOR-004 were re-randomized to either a weekly or alternate-weekly regimen of ESA. After 36 weeks (i.e., 12 weeks into MOR-005), 55 patients (98.2%) remained in the study; at the time of the data cut-off, 26 (46.4%) patients had completed 48 weeks of follow-up (i.e., 24 weeks in MOR-004 and 24 weeks in MOR-005). In Part II (which is ongoing, and not reported in this review, as insufficient data were available), all patients were transitioned to the weekly ESA regimen. While the MOR-005 Part I data can be considered only supportive at best, the cohort of patients receiving weekly ESA throughout MOR-004 and into MOR-005 appeared to maintain a similar 6MWT distance at week 48 as at week 24 in MOR-004. Interestingly, however, former placebo patients who transitioned to weekly ESA in MOR-005 appeared to achieve minimal improvements at the end of MOR-005 Part I. The reason for this is unclear, and it may represent a chance finding. More insights into the long-term efficacy of ESA may emerge as further data from MOR-005 are reported over the coming years.

The clinical expert consulted by CDR indicated that ESA will likely be offered as a treatment to any patient with MPS IVA, as no specific treatment existed for MPS IVA prior to the approval of ESA. How clinicians will determine responders from non-responders is less clear; likewise, it is unclear under what circumstances, if any, ESA may be discontinued in the event of an equivocal or suboptimal response to therapy.

4.2.2 Harms

Patient input for this submission indicated that patients would be willing to tolerate SAEs in order to experience benefit from therapy (APPENDIX 1: PATIENT INPUT SUMMARY). Overall, AEs in MOR-004 were common, but not different in frequency between ESA and placebo (96.6% versus 96.6%). The most common (> 10%) AEs with ESA treatment, which were more frequent than with placebo, were largely infusion-associated reactions, and included vomiting, pyrexia, headache, nausea, abdominal pain, diarrhea, oropharyngeal pain, otitis media, dizziness, dyspnea, gastroenteritis, and chills. The clinical expert consulted by CDR indicated that infusion-associated reactions are readily managed in a clinical setting and would be expected to lessen with repeated exposure to therapy. SAEs were more common with ESA treatment than with placebo (15.5% versus 3.4%), with infections and infestations accounting for more than half of SAEs in the ESA group and none in the placebo group. There were no withdrawals due to AEs and no deaths reported during the trial. The fact that none of the patients enrolled in MOR-004 discontinued due to AEs suggests that ESA may be reasonably well tolerated, and may also attest to the apparent willingness expressed in the patient input to endure adverse effects for a beneficial therapy.

To this point, the safety profile of ESA observed in MOR-005 appears similar to that observed in MOR-004 in terms of tolerability and the type of AEs being reported; no new safety signals have been identified from these data.

Frequently encountered during MOR-004 were AEs that the clinical expert consulted by CDR considered to be reflective of infusion-related reactions. The expert indicated that these reactions were manageable in a clinic setting and also suggested there may be some attenuation of these reactions with time, although the available data from MOR-004 cannot corroborate this, as safety events were not presented at various time points. The results of the open-label extension study MOR-005 (Part I) suggest a possible reduction in infusion-related reactions requiring discontinuation or interruption of treatment compared with MOR-004; however, a definitive interpretation in this regard is difficult, as data from the core trial and its extension cannot validly be compared directly.

ESA treatment requires weekly infusions, which puts a potential burden on patients because it could mean time away from work or school. However, patient input for this submission indicated that patients were willing to give up one day per week to receive the drug by infusion, if treatment meant disease stabilization and the possibility of undergoing fewer disease-related procedures and missing less school or work (APPENDIX 1: PATIENT INPUT SUMMARY). Hence, the mode of administration does not appear to be a significant impediment.

5. CONCLUSIONS

In a single RCT, ESA once weekly was shown to improve the primary efficacy outcome of change from baseline in 6MWT compared with placebo in patients aged five years of age or older with a confirmed diagnosis of MPS IVA. Although 6MWT is an accepted outcome for MPS IVA trials by regulatory authorities, the clinical importance of this result is unclear due to the lack of MCID in MPS IVA, and uncertain association with outcomes of importance to patients with MPS IVA, such as pain, fatigue, mobility, disease progression, and the need for surgical intervention. Results were either not statistically significant, or statistical comparisons were not made, for other outcomes of interest to this review, including the 3MSCT, urine KS, PFTs, anthropometry (e.g., height), requirement for wheelchair use, and measures of functional capacity. No data were available for quality of life, survival, or disease progression.

ESA treatment was more commonly associated with vomiting, pyrexia, headache, nausea, abdominal pain, diarrhea, oropharyngeal pain, otitis media, dizziness, dyspnea, gastroenteritis, and chills versus placebo. SAEs were more frequent with ESA treatment and most often classified as infections and infestations. There were no withdrawals due to AEs or deaths reported during the trial. No additional safety signals were identified from the data in the open-label extension trial (MOR-005).

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on input from patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

The Isaac Foundation for MPS Treatment and Research provides funding for research toward a cure for mucopolysaccharidosis (MPS) and support for families of individuals with MPS, and advocates to government for coverage of MPS treatments. The Isaac Foundation has received regular sponsorship grants from BioMarin Pharmaceuticals, Shire Pharmaceuticals, and Janssen Pharmaceuticals for fundraising events for their research programs. It declared no conflict of interest in the preparation of this submission.

The Canadian Society for Mucopolysaccharide & Related Diseases Inc. (the Canadian MPS Society) provides support to individuals and families affected with MPS. It also provides education to medical professionals and the general public about MPS, and raises funds for research. The society receives unrestricted grants and event sponsorships from Genzyme Canada, Shire Canada, and BioMarin Pharmaceuticals. It declared no conflict of interest in the preparation of this submission.

2. Condition- and Current Therapy-Related Information

Information was compiled through interviews with patients and families affected by mucopolysaccharidosis IVA (MPS IVA, also known as Morquio A syndrome) collected through telephone and in-person conversations as well as through regional meetings, a national family conference, and an electronic survey of patients affected by MPS IVA and their caregivers. Information was also collected through published and printed sources, clinical trial data, and discussion with the lead investigator for a Vimizim trial in Canada.

MPS IVA has a profound impact on all parts of a patient's life, given the progressive nature of the disease and the range of sequelae of the enzyme deficiency. MPA IVA leads to hernias, chronic ear infections, hearing impairment, corneal clouding, diarrhea, heart disease, respiratory disease, sleep apnea, hyperflexibility of joints, dysostosis multiplex, spinal stenosis leading to spinal cord compression, and short stature.

Effects on endurance and bone and joint disease are identified as having the most significant impact on a patient's quality of life. Endurance can be affected by the disease's impact on the heart, bones, and pulmonary function. Patients also reported that pain — particularly in the spine, hips and knees — had a negative impact on their quality of life. Patients may initially be able to do daily activities such as biking, skating, walking, dressing themselves, and grocery shopping, but as their condition progresses, patients are increasingly reliant on caregivers and mobility aids. Patients report difficulty with self-care (due to difficulty reaching the back of their heads), opening doors (due to decreased wrist strength), holding items, and general mobility (due to short stature, pain, hyperflexibility, skeletal dysplasia, and respiratory disease). All patients interviewed reported limitations in walking long distances and climbing stairs.

Social isolation was also reported as a consequence of MPS IVA, because of limitations in the ability to interact with peers in sporting, school, and social activities due to poor endurance, use of mobility aids,

or being confined to a wheelchair. Extra time is required for planning, scheduling, and executing daily activities.

Caregivers face significant challenges in caring for patients with MPS IVA. Those surveyed reported financial, emotional, and relationship stress. Some of the financial stress comes from costly home renovations and devices. Patients can require medical interventions, long hospital stays, many surgical appointments, and repeated appointments with specialists; caregivers sacrifice their own time to provide support in these areas. Patients also require assistance for daily activities due to mobility restrictions and limitations in dexterity.

To date, no treatment has been available specifically for MPS IVA; treatment has been symptomatic to address the consequences of the disease. Treatments have addressed the sequelae listed above, and include hernia repair, hearing aids, corrective lenses, and continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP). Surgical interventions are common, with 100% of respondents in one patient group reporting a history of orthopaedic surgery — in some cases up to six previous surgeries — which include knee stapling, hip replacement, spinal fusion, and spinal cord decompression. The subsequent post-surgical care can pose a burden on patients and caregivers, where significant pain, reduced mobility, and prolonged recovery times lead to a significant amount of care required.

3. Related Information About the Drug Being Reviewed

Patients express a desire to see disease progression stabilized or slowed. An expectation from patients and caregivers is that an improvement in mobility from treatment will improve patients' quality of life. An increase in growth and a reduced risk of cervical cord compression were noted as potential benefits of treatment and as filling an unmet need. Patients said they are willing to accept serious adverse events (SAEs) in order to experience the benefits. They are willing to spend a day a week receiving infusion therapy, recognizing it would mean less time required for other procedures if the disease had stabilized with treatment. They anticipate that improvements in the condition could lead to fewer procedures overall and less time away from school or work.

Patients who received the treatment reported improvements in endurance and stabilization in their condition, and did not report any major adverse events (AEs). Patients reported increases in weight, strength, height, and overall energy levels. They also noted improved respiratory symptoms and reduced ear and upper respiratory infections. There were also improvements in activity level, including increases in walk distance, resumption of swimming, and an ability to complete simple errands without a wheelchair. Patients and caregivers also reported a renewed sense of hope.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 15, 2014
Alerts:	Search updated biweekly (every other week) until January 21, 2015.
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
	MEDLINE Search
1	(Vimizim* or elosulfase alfa or rhGALNS* or rGALNS* or BMN-110 or BMN110 or UNII-ODJ69JZG85 or UNIIODJ69JZG85).ti,ab,ot,sh,hw,rn,nm.
2	(recombinant adj3 (N-acetylgalactosamine-6-sulfatase or GALNS)).ti,ab,ot,sh,hw,rn,nm.
3	(9025-60-9 or 9079-83-8).rn,nm.
4	or/1-3
5	4 use pmez
	Embase Search
6	*elosulfase alfa/
7	(Vimizim* or elosulfase alfa or rhGALNS* or rGALNS* or BMN-110 or BMN110 or UNII-ODJ69JZG85 or UNIIODJ69JZG85).ti,ab.
8	(recombinant adj3 (N-acetylgalactosamine-6-sulfatase or GALNS)).ti,ab.
9	or/6-8
10	9 not conference abstract.pt.
11	10 use oemezd
	Combine Results, Remove Duplicates, Remove Animal/Non-Human Studies
12	5 or 11
13	remove duplicates from 12
14	exp animals/
15	exp animal experimentation/ or exp animal experiment/
16	exp models animal/
17	nonhuman/
18	exp vertebrate/ or exp vertebrates/
19	animal.po.
20	or/14-19
21	exp humans/
22	exp human experimentation/ or exp human experiment/
23	human.po.
24	or/21-23
25	20 not 24
26	13 not 25

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 3 – 8, 2014
Keywords:	elosulfase alfa (Vimizim) and synonyms Mucopolysaccharidosis type IVA (Morquio syndrome) and synonyms
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

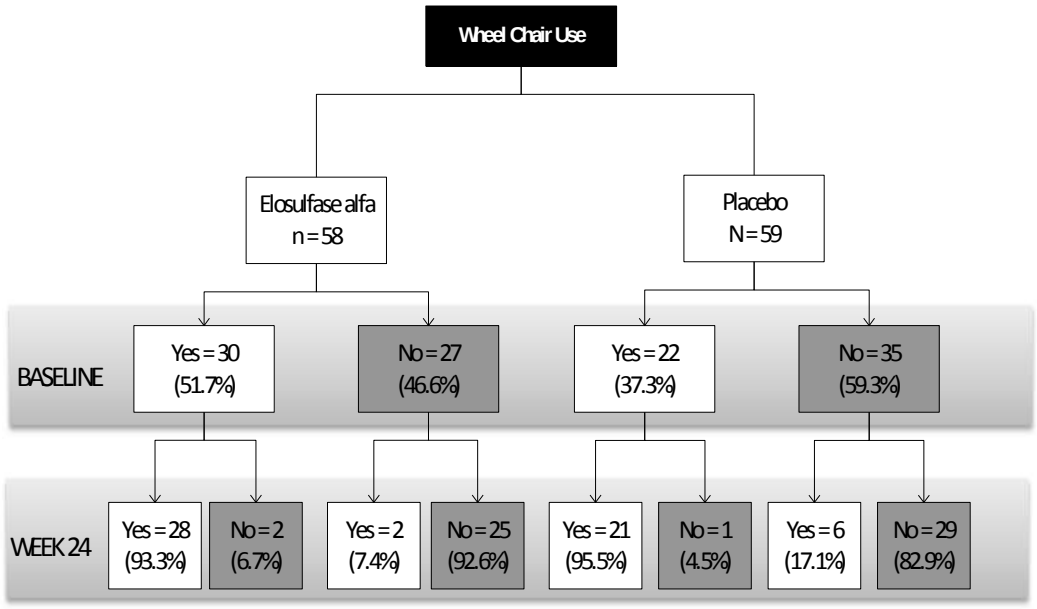
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
No potentially relevant reports were excluded.	

APPENDIX 4: DETAILED OUTCOME DATA

FIGURE 2: WHEELCHAIR USE AT BASELINE AND WEEK 24



Source: MOR-004 Clinical Study Report.[12]

TABLE 9: SUMMARY OF SIX-MINUTE WALK TEST BY SUBGROUPS: AGE, BASELINE SIX-MINUTE WALK TEST, GEOGRAPHIC REGION

6MWT (m)	MOR-004	
Age group: 5 to 11 years	**ESA**	**Placebo**
N	32	30
Baseline — mean (SD)	228.9 (67.1)	238.4 (56.4)
Week 24 — mean (SD)	263.6 (69.6)	259.2 (79.4)
Week 24 — change from baseline		
LS mean change difference from placebo (95% CI)	13.8 (–11.5 to 39.1)	
P value[a]	0.2844	
Age group: 12 to 18 years		
N	16	15
Baseline — mean (SD)	187.3 (67.9)	196.2 (77.2)
Week 24 — mean (SD)	230.2 (91.9)	190.5 (78.5)
Week 24 — change from baseline		
LS mean change difference from placebo (95% CI)	48.2 (12.4 to 84.0)	
P value[a]	0.0086	
Interaction *P* value[b]	0.1224	
Age group: ≥ 19 years		
N	10	14
Baseline — mean (SD)	150.7 (88.6)	171.8 (68.0)
Week 24 — mean (SD)	180.1 (103.1)	190.4 (69.5)

6MWT (m)	MOR-004	
Week 24 — change from baseline		
LS mean change difference from placebo (95% CI)	10.4 (–30.9 to 51.8)	
P value[a]	0.6194	
6MWT: ≤ 200 m		
N	23	23
Baseline — mean (SD)	126.1 (53.3)	136.9 (37.6)
Week 24 — mean (SD)	179.4 (91.4)	149.9 (50.0)
Week 24 — change from baseline		
LS mean change difference from placebo (95% CI)	40.4 (11.0 to 69.8)	
P value[a]	0.0074	
Interaction *P* value[c]	0.1232	
6MWT: > 200 m		
N	35	36
Baseline — mean (SD)	255.1 (33.6)	259.8 (33.8)
Week 24 — mean (SD)	279.8 (55.3)	273.6 (61.4)
Week 24 — change from baseline		
LS mean change difference from placebo (95% CI)	10.8 (–12.8 to 34.4)	
P value[a]	0.3657	
North America		
N	15	16
Baseline — mean (SD)	171.3 (59.3)	213.7 (57.0)
Week 24 — mean (SD)	227.2 (75.0)	224.3 (67.0)
Week 24 — change from baseline		
LS mean change difference from placebo (95% CI)	43.4 (7.5 to 79.3)	
P value[a]	0.0180	
Interaction *P* value[d]	0.4228	
Interaction *P* value[e]	0.1393	

6MWT = six-minute walk test; CI = confidence interval; ESA = elosulfase alfa; FVC = forced vital capacity; KS = keratan sulfate; LS = least squares; m = metres; min = minute; SD = standard deviation.
[a] *P* value determined by t-test from ANCOVA model.
[b] Age 12 to 18 years versus age 5 to 11 years.
[c] 6MWT > 200 m versus 6MWT ≤ 200 m.
[d] Europe versus North America.
[e] Other versus North America.
Source: MOR-004 Clinical Study Report.[12]

TABLE 10: DESCRIPTIVE SUMMARY OF WEIGHT AND HEIGHT AT BASELINE AND WEEK 24

Anthropometric Outcome	MOR-004			
	ESA (n = 58)	ESA (n = 44)[a]	Placebo (n = 59)	Placebo (n = 40)[a]
Standing height (cm)				
Baseline				
Mean (SD)	101.3 (13.1)	100.1 (12.1)	105.5 (16.8)	101.7 (12.3)
Week 24				
Mean (SD)	102.7 (13.0)	101.8 (11.9)	106.3 (16.8)	102.5 (12.4)
Change from baseline[b] to week 24				
Mean (SD)	1.2 (1.5)	1.6 (1.4)	0.9 (1.3)	1.1 (1.4)
Standing height z-score				
Baseline				
Mean (SD)	–6.4 (2.6)	–5.6 (2.1)	–6.0 (2.8)	–5.1 (2.2)
Week 24				
Mean (SD)	–6.4 (2.5)	–5.7 (2.0)	–6.1 (2.6)	–5.4 (2.1)
Change from baseline[b] to week 24				
Mean (SD)	–0.0 (0.3)	–0.0 (0.3)	–0.1 (0.3)	–0.2 (0.3)
Weight (kg)				
Baseline				
Mean (SD)	22.9 (10.5)	20.3 (8.4)	25.4 (11.5)	20.6 (6.4)
Week 24				
Mean (SD)	23.5 (10.1)	21.0 (7.8)	26.3 (11.9)	21.7 (7.5)
Change from baseline[b] to Week 24				
Mean (SD)	0.7 (1.7)	0.7 (2.0)	1.1 (1.5)	1.2 (1.4)

ESA = elosulfase alfa; SD = standard deviation.
[a] Patients who still had growth potential (males aged ≤ 18 years and females ≤ 15 years).
[b] Change is equal to current value minus baseline value.
Source: MOR-004 Clinical Study Report.[12]

TABLE 11: DESCRIPTIVE SUMMARY OF MPS HAQ DOMAIN SCORES AT BASELINE AND WEEK 24

MPS HAQ Domain Score	MOR-004	
	ESA (n = 58)	Placebo (n = 59)
Self-care		
Baseline		
Mean (SD)	3.7 (2.7)	3.5 (2.3)
Week 24		
Mean (SD)	3.4 (2.6)	3.1 (2.3)
Change from baseline[a] to Week 24		
Mean (SD)	–0.3 (0.9)	–0.4 (1.2)
Mobility		
Baseline		
Mean (SD)	4.6 (2.9)	4.5 (2.7)
Week 24		
Mean (SD)	3.8 (2.6)	4.0 (2.7)
Change from baseline[a] to Week 24		
Mean (SD)	–0.7 (1.6)	–0.5 (1.8)
Caregiver assistance		
Baseline		
Mean (SD)	27.5 (11.1)	26.1 (9.1)
Week 24		
Mean (SD)	24.9 (8.6)	24.9 (8.9)
Change from baseline[a] to Week 24		
Mean (SD)	–2.3 (7.0)	–1.1 (5.8)

ESA = elosulfase alfa; MPS HAQ = Mucopolysaccharidosis Health Assessment Questionnaire; SD = standard deviation.
[a] Change is equal to current value minus the baseline value.
Source: MOR-004 Clinical Study Report.[12]

TABLE 12: INCIDENCE OF ADVERSE EVENTS DURING INFUSION REQUIRING MEDICAL INTERVENTION

	MOR-004	
AEs	**ESA (n = 58)**	**Placebo (n = 59)**
Patients with infusion interrupted or discontinued due to an AE that also required medical intervention[a]	13 (22.4)	0
Number of patients with infusions interrupted	11 (19.0)	0
Number of patients with infusions discontinued	3 (5.2)	0
Medical intervention		
IV antihistamines	10 (17.2)	0
IV steroids	6 (10.3)	0
IV fluids	5 (8.6)	0
Oxygen	2 (3.4)	0

AE = adverse event; ESA = elosulfase alfa; WHO = World Health Organization.
[a] Only AEs during interrupted or discontinued infusions were considered. For infusion interruption, the infusion was completed; for infusion discontinuation, the infusion was not completed. Medical intervention was defined as one or more of the following: IV antihistamine, IV steroids, IV fluids, or oxygen, as determined according to WHO drug coding.
Source: MOR-004 Clinical Study Report.[12]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To summarize the available evidence on the validity of the following outcome measures reported in the studies of ESA:

- Six-minute walk test (6MWT)
- Urine keratan sulfate (KS)
- Forced vital capacity (FVC)
- Mucopolysaccharidosis (MPS) Health Assessment Questionnaire (HAQ).

Findings

Six-minute walk test

The 6MWT is a supervised test that measures the distance a patient can walk on a hard flat surface over a six-minute period.[20] A specific protocol outlining training, level of support provided to the patient, and standardization of distance available for the patient to walk (30 m) is provided by the American Thoracic Society (ATS).

A search was conducted for validation studies of the 6MWT in mucopolysaccharidosis IVA (MPS IVA; also known as Morquio A syndrome) and other MPS conditions. No studies were identified. The 6MWT has been used and validated in multiple adult patient populations with cardiopulmonary conditions (e.g., heart failure, chronic obstructive pulmonary disease, pulmonary hypertension).[20] Multiple studies have also established a proposed minimal clinically important difference (MCID) in these populations. Reported distances associated with a noticeable functional improvement range from 54 m in patients with stable chronic obstructive pulmonary disease (COPD) and 43 m in patients with heart failure. It should be noted that patients in these populations are significantly older than the majority of patients enrolled in MPS-004 and MPS-005.

It is recognized that functional impairment in MPS IVA arises from musculoskeletal sequelae of the disease rather than from a cardiopulmonary source, thus a search was conducted on the validation of the 6MWT in rheumatological and other musculoskeletal conditions. The only study identified was one small trial assessing the 6MWT in patients with systemic sclerosis, in which abnormal 6MWT values failed to correlate with most independent markers of disease activity (e.g., disease severity scores, health assessment questionnaires).[21]

Initial improvements in the 6MWT should be interpreted with caution, as there has been a well-documented learning effect in patients previously unfamiliar with the test.[22] Motivation, encouragement, and co-operation can have a significant positive impact on the results, and the magnitude of these effects could be comparable to the effect of interventions.[23,24] This could be of special concern in situations where blinding is not present or is compromised.

A systematic review of the literature on the 6MWT in the pediatric population across nine conditions, including those with musculoskeletal disorders, identified several issues associated with use of the test in this population.[25] Of the trials included, there was variability in adherence to the ATS statement with regard to distance used and degree of coaching, assistance, and encouragement. This can have a significant impact on results, as the authors noted that children have difficulty completing tasks that have longer durations and tend to respond better with constant verbal encouragement. In patients with juvenile idiopathic arthritis, there was poor correlation between 6MWT results and peak oxygen intake,

suggesting that the 6MWT has limited ability to assess aerobic capacity in this population. MCID values reported in the systematic review ranged from 36 m in patients with spina bifida to 68 m in obese patients.

Other studies have found that the age, height, and weight of a child can have an impact on the distance travelled in six minutes. This may affect 6MWT results obtained from trials of longer duration.[26,27]

It should be noted that the 6MWT has been used as an outcome measure in trials involving other lysosomal storage disorders (MPS II and VI). However, as described by the FDA, the pathophysiology of these conditions is different from that of MPS IVA, particularly with respect to the larger degree of cardiopulmonary involvement in MPS II and VI.[28] Nevertheless, the FDA accepted that the 6MWT is an acceptable outcome for MPS IVA, as it was acknowledged to incorporate some functional outcomes affected by the disease, even though other aspects (such as pain and fatigue) are not adequately captured.[17]

Urine keratan sulfate

KS is a glycosaminoglycan (GAG), also known as a mucopolysaccharide. The presence of elevated levels of KS in the urine, in conjunction with other clinical data and laboratory testing, can aid the diagnosis of MPS IVA.[6] However, it is not sufficient for diagnosis, as urine KS values can be normal in patients with MPS IVA.[6,29] Urine KS is measured from the first morning void and is normalized to serum creatinine. Urine KS levels, if abnormal, are highest at younger ages and decline over time. Two studies assessed whether urine KS correlated with disease severity in MPS IVA. One trial of 55 patients was unable to find such a correlation.[30] A second trial reported that even after adjustments for age, higher levels of urine KS (> 20 mcg/mg creatinine) were correlated with disease markers such as shorter height. However, the cut-off to describe an abnormally high level of urine KS was determined based on scatterplot smoothing from correlations between urine KS and 6MWT, which may have significant limitations based on the issues with using 6MWT in the MPS IVA population as described above.

Pulmonary function tests

Forced expiratory volume in 1 second (FEV_1) is the volume of air that, after a full inspiration, can be forcibly expired in one second (standardization of spirometry). FVC is the maximal volume of air exhaled forcefully after a maximal inhalation. Maximum voluntary ventilation (MVV) is the volume of air expelled over a specified period of time, usually 12 seconds in normal individuals. While FEV_1 and FVC are commonly used in studies and clinical practice, the MVV is not frequently reported due to its high correlation with FEV_1; it is often calculated by multiplying FEV_1 by a constant rather than measured directly. The ATS notes that in certain neuromuscular disorders, MVV may be relevant as there may be a disproportionate reduction in MVV in relation to FEV_1.

An important issue relevant to the interpretation of spirometric values in the MPS IVA population is the relationship between standing height and lung volumes.[20] Standing height is a significant variable in the interpretation of lung volumes, yet it is severely affected in MPS IVA. In children and adolescents, lung volumes can lag behind standing height growth rates. Therefore, an adjustment in reference equations may be required. Additional factors that may affect interpretation of values can include age, as lung function plateaus in the third decade of life and declines by an expected 30 mL/year thereafter. A search for evidence on the validity of pulmonary function tests (PFTs) in MPS IVA yielded no studies assessing the degree to which PFTs correlate to disease severity.

The ATS suggests an MCID for increases in FEV_1 and FVC of 12% to 15%.[20] Changes of less than 8% can be within the range of measurement variability. However, these values have been suggested in patients with respiratory disease responsive to bronchodilators; hence, their applicability to the MPS IVA population is uncertain. No studies were identified that assessed the MCIDs of FEV_1 or FVC in patients with MPS IVA.

MPS health assessment questionnaire

The MPS Health Assessment Questionnaire (HAQ) assesses mobility and self-care tasks in MPS patients.[10,18] It consists of 52 questions distributed over three domains, the items within which are scored on a 10-point scale (0 = not difficult at all; 10 = extremely difficult): self-care (27 items, such as bathing, grooming, eating, drinking, dressing, brushing teeth); mobility (12 items, such as walking and stair climbing); and caregiver assistance (13 items).[12,18] No studies have validated the MPS HAQ in the MPS IVA population or other MPS populations. Since it was originally developed for use in MPS I disease, there has been some concern that the MPS HAQ may lack measurement sensitivity (i.e., ability to detect changes) in MPS IV disease.[5] There are no published MCIDs for the MPS HAQ.

Summary

There are limitations to the validity of several key outcome measures used in the trials of ESA. No studies validating the 6MWT in MPS IVA were identified. The correlation of the 6MWT with disease severity is uncertain outside of cardiopulmonary conditions, which is problematic for its application to MPS IVA due to the predominantly musculoskeletal pathophysiology of the condition. Use of the 6MWT in a pediatric population has additional limitations due to the potential impact of height, age, and weight on performance. Nevertheless, the FDA accepted the 6MWT as an outcome for MPS IVA studies despite its limitations. The value of the measurement of PFTs in the MPS IVA population is unclear due to the lack of data assessing correlation between these tests and disease severity or functional improvement. Given the rare and heterogeneous presentation of MPS IVA and the consequent difficulties in developing and validating tools for this population, the lack of validated instruments to measure disease severity, progression, or improvement with treatment in patients with MPS IVA is perhaps not surprising. However, it does impair the ability to judge the effectiveness of treatments such as ESA.

APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY

Objective

To summarize and critically appraise MOR-005,[31] an open-label extension study of MOR-004.

Study characteristics

Study MOR-005 was a phase 3, two-part extension trial of MOR-004 designed to assess the long-term safety and efficacy of elosulfase alfa (ESA) in mucopolysaccharidosis IVA (MPS IVA; also known as Morquio A syndrome). Outcomes remained identical to those analyzed in MOR-004. Part 1 was a 24-week blinded follow-up to MOR-004, in which all patients received active treatment with ESA on either a weekly or every-other-week dosing schedule. Patients who were receiving ESA in MOR-004 continued with their assigned dosing schedule, while patients in the placebo group were re-randomized to ESA 2 mg/kg/week or 2 mg/kg/every other week. In Part 2, all patients began receiving the weekly dose of ESA in an open-label fashion (based on the results of MOR-004, which supported this dose). The trial is scheduled to continue until 2017, and has a planned follow-up of up to a total of 240 weeks.

Patients who completed MOR-004 totalled 175, with 173 enrolling in MOR-005. One patient withdrew consent, and three patients are waiting for a treatment infusion centre to open in their hometowns, leaving 169 patients receiving the drug and available for analysis of MOR-005 Part 1. The proportions of patients completing trial assessments in MOR-005 over time are summarized in Table 13.

TABLE 13: PATIENT FOLLOW-UP IN MOR-005

	PBO-QOW n = 29	PBO-QW n = 29	QOW-QOW n = 59	QW-QW n = 56
Duration of follow-up in MOR-005 (mean, weeks)	28.02	27.02	26.79	27.55
Patients with assessments at week 36,[a] n (%)	27 (93.1%)	25 (86.2%)	51 (86.4%)	48 (85.7%)
Patients with assessments at week 48,[a] n (%)	14 (48.3%)	12 (41.4%)	26 (44.1%)	26 (46.4%)

ESA = elosulfase alfa; PBO-QOW = patients who initially received placebo in MOR-004 and ESA 2mg/kg/every other week in MOR-005; PBO-QW = patients who initially received placebo in MOR-004 and ESA 2mg/kg/every week in MOR-005; QOW-QOW = patients who received ESA 2 mg/kg/every other week in both MOR-004 and MOR-005; QW-QW = patients who received ESA 2mg/kg/weekly in both MOR-004 and MOR-005.

[a] From MOR-004 baseline; incomplete follow-up due not to withdrawals but to cut-offs for provision of data.

Results

As MOR-005 is an ongoing study, only descriptive statistics were reported for each arm; no between-treatment comparisons were performed. Survival was not an outcome of this trial; however, no patients died during follow-up. Wheelchair usage was not reported. The results of MOR-005 Part 1 are summarized in Table 14. While no comparative statistical results were reported, there were no indications of substantial changes between week 24 and week 48 within groups, or differences between groups at week 48. Interestingly, patients who switched from placebo in MOR-004 to weekly ESA in MOR-005 appeared to have minimal improvement in the six-minute walk test (6MWT) (~1 m), and the magnitude of improvement in this parameter among patients switched from placebo to ESA every other week was modest (~14 m). However, in light of the small sample sizes for these groups and the lack of inferential statistics, it is not possible to draw definitive conclusions from these data.

TABLE 14: EFFICACY OUTCOMES IN MOR-005

Timepoint	PBO-QOW n = [redacted]	PBO-QW n = [redacted]	QOW-QOW n = [redacted]	QW-QW n = [redacted]
6MWT — change from baseline[a] (m), mean (SD)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
3MSCT — change from baseline[a] (stairs/min), mean (SD)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
FVC — change from baseline[a] (L), mean (SD)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 — change from baseline[a] (L), mean (SD)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
MVV — change from baseline[a] (L), mean (SD)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Standing height (cm), mean (SD)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Standing height z-score — mean (SD)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to week 48[a]	[redacted]	[redacted]	[redacted]	[redacted]

6MWT = six-minute walk test, 3MSCT = three-minute stair-climb test; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; MVV = maximum voluntary ventilation; PBO-QOW = patients who initially received placebo in MOR-004 and ESA 2mg/kg/every other week in MOR-005; PBO-QW = patients who initially received placebo in MOR-004 and ESA 2mg/kg/every week in MOR-005; QOW-QOW = patients who received ESA 2mg/kg/every other week in both MOR-004 and MOR-005; QW-QW = patients who received ESA 2mg/kg/weekly in both MOR-004 and MOR-005; SD = standard deviation.
[a] From MOR-004 baseline. Week 24 results represent means for patients who eventually completed the week 48 assessment. Therefore, these results may differ from MOR-004 end point results.

Harms

Adverse events (AEs) reported in MOR-005 Part 1 were similar in nature and frequency to those reported in MOR-004; there were no apparent differences in event rates between groups with respect to the risk of any AE or for most individual AEs (Table 15). However, the risk of serious adverse events (SAEs) appeared to be lowest among patients originally randomized to weekly ESA in MOR-004 (and continuing this therapy in MOR-005).

TABLE 15: ADVERSE EFFECT OUTCOMES REPORTED WITH > 10% FREQUENCY IN MOR-005

	PBO-QOW n = [redacted]	PBO-QW n = [redacted]	QOW-QOW n = [redacted]	QW-QW n = [redacted]
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; PBO-QOW = patients who initially received placebo in MOR-004 and ESA 2mg/kg/every other week in MOR-005; PBO-QW = patients who initially received placebo in MOR-004 and ESA 2mg/kg/every week in MOR-005; QOW-QOW = patients who received ESA 2mg/kg/every other week in both MOR-004 and MOR-005; QW-QW = patients who received ESA 2mg/kg/weekly in both MOR-004 and MOR-005; SAE = serious adverse event.

Limitations

The lack of a control group in MOR-005 limits the ability to understand the impact of long-term ESA treatment on disease progression (e.g., the need for wheelchair or walking aids, surgeries, etc.). Protocol violations were common in MOR-005 Part 1, with 94.2% of patients having a minor protocol violation and 36.4% of patients having a major protocol violation. Although 169 of 173 patients continued assigned therapy through 48 weeks post-MOR-004 baseline, follow-up data were available for less than 50% of patients at 48 weeks. While this appears to be an administrative issue related to cut-offs for data provision, it represents a possible source of bias due to the possibility that the subset of patients with follow-up data available differed from those for whom data were unavailable.

Summary

The results reported to date from Part 1 of the MOR-005 extension study suggest that the initial response to ESA observed in MOR-004 may be maintained at 48 weeks' follow-up among patients who persist with therapy. These results should be interpreted in light of the fact that most patients had at least one protocol violation (and approximately one-third had a serious protocol violation) in MOR-005 Part 1. As well, follow-up data were available for less than half of patients at 48 weeks.

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