May 2016

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
Dosage form	2 mg/kg IV infusion once weekly
NOC date	July 2, 2014
Manufacturer	BioMarin Pharmaceutical Canada Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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ABBREVIATIONS

3MSCT	three-minute stair-climb test
6MWT	six-minute walk test
AE	adverse event
CDR	CADTH Common Drug Review
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
EQ-5D	EuroQol 5-Dimensions Health-Related Quality of Life questionnaire
ESA	elosulfase alfa
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GAG	glycosaminoglycan
GALNS	N-acetylgalactosamine-6-sulfatase
HRQoL	health-related quality of life
ITT	intention-to-treat (population)
KS	keratan sulfate
LS	least squares
MCID	minimal clinically important difference
MPP	modified per-protocol
MPS	mucopolysaccharidosis
MPS HAQ	mucopolysaccharidosis Health Assessment Questionnaire
MPS IVA	mucopolysaccharidosis type 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

EXECUTIVE SUMMARY

Introduction

Mucopolysaccharidosis type IVA (MPS IVA), or 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) principally found in skeletal and cartilaginous tissue.[1] The disorder causes GAGs to 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. Currently, 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.

Elosulfase alfa (ESA) 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. It is dosed at 2 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.

In March 2015, the CADTH Canadian Drug Expert Committee (CDEC) issued a "do not list" recommendation for ESA. Key reasons for the recommendation included uncertain clinical relevance for improvement in six-minute walk test (6MWT) distance and failure to identify improvement in other clinical end points, including pain reduction, fatigue, disease progression, or need for surgical intervention.[6] The manufacturer has provided new clinical data, including [redacted]; ad-hoc responder analyses based on MOR-004; long-term (120 weeks) results in terms of endurance and pulmonary function from an MOR-005 extension trial; and results from MOR-007, which evaluated the use of ESA in children younger than five years.

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

Results and interpretation

No studies meeting the inclusion criteria of the systematic review were identified. However, the CADTH Common Drug Review (CDR) reviewed the following clinical information included in the resubmission.

Clinical relevance of the six-minute walk test results

In MOR-004, change in 6MWT distance was the primary efficacy outcome. While frequently utilized in cardiopulmonary conditions, the relevance and validity of this outcome for MPS IVA patients are uncertain. Furthermore, the 6MWT minimal clinically important difference (MCID) value in MPS IVA patients is unknown. The mean percentage changes from baseline (± standard deviation [SD]) at week

24 were 8.7% (± 28.8) and 23.9% (± 44.8) for placebo and weekly ESA, respectively (mean difference of 15.2%). [redacted]. However, CDR identified several limitations concerning the manufacturer's estimation. The manufacturer cited a post-hoc Delphi consensus panel that estimated a more conservative MCID of 15%.

Multi-Domain Responder Analysis
This was a post-hoc analysis based on the per-protocol results of MOR-005 at 72 weeks for patients who received weekly ESA in MOR-004 and MOR-005. [redacted].

The main limitation of this analysis was in the definition of responders; the manufacturer considered patients who had any value of improvement to be responders. Another limitation of multi-domain responder analysis was that it excluded [redacted] of patients who missed doses or had surgeries. The manufacturer did not provide information about the excluded patients who might potentially be considered non-responders.

Long-term safety and efficacy profile of elosulfase alfa
The manufacturer provided new data for up to 120 weeks (96 weeks in MOR-005) of treatment with ESA based on endurance and pulmonary function.

Patients treated with ESA continued to show improvement in 6MWT distance until 72 weeks of treatment; after this time point, the 6MWT seemed to decline to values approaching those at baseline of MOR-005. [redacted].

The improvements in forced vital capacity (FVC) observed at week 24 were further improved by a mean (standard error [SE]) increase of 0.08 (0.02) L (8.6%) by week 120. The improvements are non-statistically significant compared with the MOR-005 baseline.

Efficacy and safety of elosulfase alfa in patients younger than five years
The manufacturer reported results of 15 pediatric patients younger than five years who were included in an open-label, single-group study (MOR-007). It was reported that all included patients experienced at least one adverse event (AE); among them, 13 (87%) reported drug-related AEs, including pyrexia (53%), vomiting (40%), and abdominal pain (27%). Seven patients reported a serious adverse event (SAE). No patients discontinued treatment due to AEs. There were no reported deaths.

Growth velocity results showed that cumulative growth rates remained positive for patients aged two years and older. The mean height in patients aged two years or older increased by 5.3 (± 2.1) cm from baseline to week 52, which further increased to 7.6 (± 1.9) by week 104.

Conclusions

Key concerns regarding the initial submission were uncertainty of the clinical relevance for improvement in 6MWT distance and failure to improve other clinical end points, including pain reduction, fatigue, disease progression, or the need for surgical intervention. Other concerns included limited evidence on long-term safety and efficacy, efficacy and safety in pediatric patients younger than five years, and criteria for patient selection and treatment stopping. The resubmission consisted mainly of [redacted]

[redacted], ad-hoc responder analyses based on MOR-004, and long-term (120 weeks) results in terms of endurance and pulmonary function from the MOR-005 extension trial.

No new clinical evidence met the inclusion criteria of the original systematic review. [redacted]; however, this is likely an underestimate, [redacted] closer to that reported in existing literature. The long-term efficacy data from the extension study MOR-005 showed that improvement in 6MWT and FVC continued up to 72 weeks of treatment; however, 6MWT results at 120 weeks appeared to decline to baseline values. No additional safety signals were identified for pediatric patients younger than five years in MOR-007.

1. INTRODUCTION

1.1 Disease prevalence and incidence

Mucopolysaccharidosis type IVA (MPS IVA), or 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 with 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] Extraskeletal systems adversely affected in MPS IVA include visual, auditory, respiratory, cardiovascular, and digestive systems.[8] Manifestations described in the patient group input received by the 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, though an industry-sponsored, multinational, longitudinal registry study is ongoing (MorCAP).[9] Likewise, estimates of the incidence of MPS IVA vary by region, ranging from 1 in 76,000 live births in Northern Ireland to 1 in 640,000 live births in western Australia.[8] An incidence of 1 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. Currently, 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.[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] The 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.[11] 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.[11] 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 IVA has been palliative — using a combination of medical and surgical interventions for symptom management with the goal of improving or maintaining quality of life (QoL) 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 did not report levels of evidence for each recommendation.[12]

Widespread skeletal dysplasia is the hallmark of MPS IVA,[1,2] with frequent orthopedic surgical interventions required to correct bone deformities.[2] Surgery is an inherently risky intervention in MPS IVA patients because of their complex airway management needs, which arise 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 N-acetylgalactosamine-6-sulfate sulfatase (GALNS), the enzyme responsible for breaking down the glycosaminoglycans KS and chondroitin-6-sulfate, which are 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 administered 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 (Morquio A syndrome). 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. SUBMISSION HISTORY

In March 2015, the CADTH Canadian Drug Expert Committee (CDEC) issued a recommendation that ESA not be listed. Key reasons for the recommendation included uncertain clinical relevance for improvement in six-minute walk test (6MWT) distance and failure to improve other clinical end points, including pain reduction, fatigue, disease progression, or the need for surgical intervention.[6] CDEC also noted that the initial submission lacked evidence on long-term safety and efficacy, efficacy and safety in pediatric patients under five years old, and criteria for patient selection and treatment discontinuation.

2.1 Basis of resubmission

The manufacturer provided new clinical data to support the resubmission. The resubmission was mainly based on [redacted], ad-hoc responder analyses based on MOR-004, and long-term (120 weeks) results for endurance and pulmonary function from the MOR-005 extension trial. The manufacturer also included an opinion document authored by eight Canadian clinicians specializing in pediatrics, genetics, or metabolic disorders. The main focus of this document was on treatment initiation, goals, and termination. In addition to these, the manufacturer included efficacy results in patients younger than five years from MOR-007 after 52 weeks of treatment.

3. OBJECTIVES AND METHODS

3.1 Objective

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.

3.2 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 1.

TABLE 1: 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 orthopedic)
	• Endurance
	  ○ 6MWD, 3MSCT
	• Pulmonary function
	  ○ FVC, FEV_1, MVV
	Other efficacy outcomes:
	• Growth/development
	  ○ Weight/BMI
	  ○ Standing height (children)
	• Quality of life[a]
	• Functional capacity[a]
	• Urine 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; 6MWT = six-minute walk test; AE = adverse event; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IV = intravenous; KS = keratan sulfate; MPS IVA = mucopolysaccharidosis type IVA; MVV = maximum voluntary ventilation; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Outcomes that are identified in the patient input.

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 concepts were Vimizim (elosulfase alfa) and mucopolysaccharidosis IV.

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. See Appendix 2 for the detailed search strategies.

The initial search was completed on December 10, 2015. Regular alerts were established to update the search until the CDEC meeting on April 20, 2016. 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 CADTH *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

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

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.

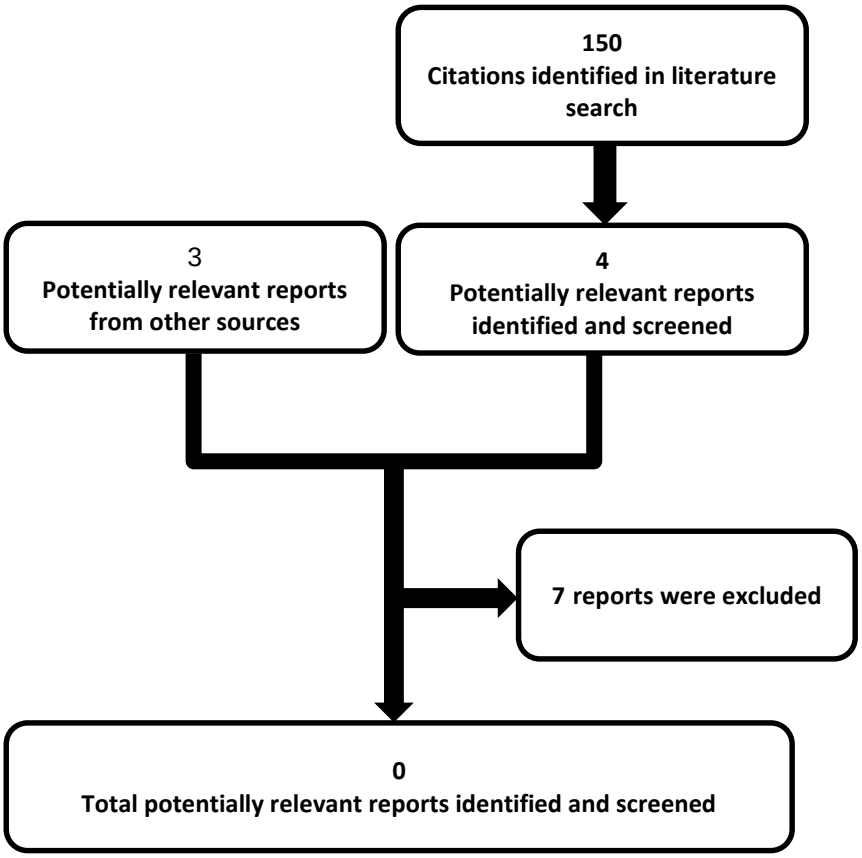
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

4. RESULTS

4.1 Findings from the literature

No studies were identified from the literature for inclusion in the systematic review (Figure 1). A list of the excluded studies and reasons for exclusion are summarized in APPENDIX 3.

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



4.2 Key clinical issues

One randomized controlled trial (RCT), MOR-004, was reviewed in the original submission and summarized in APPENDIX 4. This was a 24-week, double-blind, three-group, placebo-controlled RCT. The 177 participants were randomized in a 1:1:1 ratio to either a once a week or once every other week regimen of ESA 2 mg/kg or matching placebo. The CDR review and CDEC's deliberation focused on the Health Canada–approved regimen of weekly administration of ESA. CDEC discussed the following outcomes:

- Disease progression — assessed by the prevalence of wheelchair dependency
- 6MWT — change from baseline in total distance walked in six minutes (the change from baseline in 6MWT after 24 weeks was the primary efficacy outcome in MOR-004)
- Three-minute stair-climb test (3MSCT) — change from baseline in the number of stairs climbed per minute over three minutes
- Mucopolysaccharidosis Health Assessment Questionnaire (MPS HAQ) — an instrument used to assess changes in health-related quality of life (HRQoL) of patients with MPS
- Changes in body weight and standing height
- Pulmonary function — change from baseline in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and maximum voluntary ventilation (MVV)
- Total adverse events (AEs), serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs).

4.2.1 Clinical relevance of the six-minute walk test results

In MOR-004, ESA was not statistically different from placebo in any of the evaluated outcomes except for 6MWT. While frequently used in cardiopulmonary conditions, the clinical relevance of using the 6MWT for MPS IVA patients is uncertain in terms of its validity and correlation with meaningful clinical outcomes associated with MPS IVA. The mean changes (± standard deviation [SD]) in 6MWT from baseline at week 24 were 13.5 (± 50.6) m and 36.5 (± 58.5) m for placebo and weekly ESA, respectively. ESA was statistically superior to placebo for improvement in six-minute walking distance (adjusted least squares [LS] mean difference: 22.5 m; 95% confidence interval [CI], 4 to 41). In terms of percentage change from baseline, the mean percentage changes (± SD) at week 24 were 8.7% (± 28.8) and 23.9% (± 44.8) for placebo and weekly ESA, respectively (mean difference: 15.2%). Due to the uncertainty of the validity of the 6MWT as an outcome in this population and lack of a validated corresponding minimal clinically important difference (MCID), CDEC concluded that the clinical relevance of this finding was uncertain.

[redacted]. In addition to these analyses, the manufacturer included a published cross-sectional study to show the clinical correlation between 6MWT and HRQoL. The study assessed the correlation between patient-reported outcomes (PROs) and clinical outcomes in 24 German Morquio A patients (Lamp et al. 2015).[13]

a) Standard error of measurement

[redacted]

[redacted]

b) Lamp et al. 2015[13]

Lamp et al. conducted a cross-sectional analysis to estimate the correlation between PROs (mainly the EuroQol 5-Dimensions Health-Related Quality of Life questionnaire, 5 Levels [EQ-5D-5L]) and clinical outcomes, including 6MWT in 24 German Morquio A patients. The manufacturer included this study to show that 6MWT correlated with HRQoL. Results of the analysis showed a positive correlation between the 6MWT and the EQ-5D-5L score (r = 0.713; P = 0.0019). This correlation was shown to be strong in adult patients only (0.884), but was very weak in pediatric patients (0.212) (Table 2). In a systematic review by Bartels et al.,[14] it was shown that the 6MWT reliability and measurement errors varied largely among chronic pediatric conditions. However, none of the included studies in Bartels' review evaluated the test in Morquio A patients.[14]

These findings did not provide information about the MCID of the 6MWT. Lamp et al.[13] estimated that for every 100 m gained on the 6MWT, the EQ-5D-5L score improved by 0.2 points. None of the MOR-004 treatment groups achieved a mean gain of 100 m on 6MWT, and only 15% of patients in the weekly-treated ESA group had a > 100 m improvement.

TABLE 2: CORRELATION BETWEEN SIX-MINUTE WALK TEST AND EQ-5D-5L SCORES

Patient Group	Pearson's Coefficient of Correlation
All patients	0.713
Adult patients	0.884
Children	0.212

EQ-5D-5L = EuroQol 5-Dimensions Health-Related Quality of Life questionnaire, 5 Levels.
Source: Manufacturer submission[3] adapted from Lampe et al.[13]

c) Effect size

Effect size is a standardized measure of change achieved by dividing the difference in scores from baseline to post-treatment by the SD of the baseline scores. The effect size value represents the number of SDs by which the scores have changed from baseline to post-treatment. The manufacturer reported that an effect size of 0.2 is considered small, 0.5 moderate, and 0.8 large. [redacted]

TABLE 3: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The main limitation of this approach is considering [redacted] as a clinically meaningful value while, in fact, a half SD or effect size seems to be more universally accepted as a threshold for MCID estimation.[15,16]

4.2.2 Limited comparative efficacy data

The reviewed evidence from MOR-004 in the original submission showed that there was no statistically significant difference between ESA and placebo for improvement in the endurance of MPS IVA patients as measured by the 3MSCT. The study failed to identify that treatment with ESA improved other clinical end points, including pain reduction, fatigue, disease progression, or the need for surgical intervention. Furthermore, CDEC highlighted that there were limited or no data regarding the clinical benefit of ESA on survival, requirement for walking aids, and QoL.

The manufacturer did not provide new comparative evidence to address CDEC concerns about the limited efficacy data supporting the use of ESA in MPS IVA patients. However, the resubmission material included a "multi-domain responder analysis" to support the efficacy claims.

a) Multi-Domain Responder Analysis

This was a post-hoc analysis based on the per-protocol results of MOR-005 at 72 weeks for patients who received weekly ESA in MOR-004 and MOR-005.

The manufacturer justified this analysis by citing the multi-systemic nature of MPS IVA, arguing that treated patients might see improvement in one domain and stabilization or deterioration in another. According to the submitted material, the analysis was undertaken across two domains: endurance (as measured by 6MWT and 3MSCT) and pulmonary function (as measured by FVC and MVV). However, the manufacturer provided results of the FVC and 6MWT only. The manufacturer defined responders as patients receiving ESA treatment who demonstrated any improvement from baseline in endurance (measured using 6MWT or 3MSCT) and/or pulmonary function. Patients were classified as "multi-domain responders" if they had *any improvement* from baseline in endurance and any improvement from baseline in pulmonary function, or "single-domain responders" if they had improvements in one outcome. Patients were considered "non-responders" if they had no improvement in either outcome. [redacted].

CDR identified several issues with this analysis. The main limitation was in the definition of responders; the manufacturer considered patients who had *any value of improvement* to be responders. This definition did not include the patient's or clinician's perspective of what would be a meaningful improvement value. [redacted], while a more reasonable estimate may be one that is consistent with a 0.5 SD or moderate effect size. [redacted]

[redacted]. MCID values should have been used to determine responders in this analysis instead of including any value of improvement. The manufacturer reported the multi-domain responder analysis that was conducted by Hendriksz et al.[12] Hendriksz's analysis was based on the average of the 24-week changes from baseline in 6MWT, 3MSCT, and MVV outcome measures from the MOR-004 study. The critical point in this analysis, in contrast with the manufacturer's analysis, was that Hendriksz et al. considered responders to be those who achieved at least a 15% change for the 6MWT, a 20% change for the 3MSCT and a 20% change for MVV.[12]

Another limitation of the multi-domain responder analysis was that [redacted]. The manufacturer did not provide information about the excluded patients who might potentially be considered to be non-responders. Furthermore, the manufacturer did not report the results of 3MSCT or MVV, as was intended in the analysis description. Finally, the analysis did not include a comparative control group; and the relative rate of responders is unknown compared with the placebo treatment or the natural progression of the disease.

4.2.3 Long-term safety and efficacy profile of elosulfase alfa

At the time of the initial submission, evidence for the efficacy and safety of ESA was supported by data up to 72 weeks (24 weeks in MOR-004 and up to 48 weeks in MOR-005). CDEC commented that the long-term profile requires further evaluation. The manufacturer provided new data for up to 120 weeks (96 weeks in MOR-005) of treatment with ESA (Figure 2).

Study MOR-005 was a phase 3, two-part extension trial of MOR-004 designed to assess the long-term safety and efficacy of ESA in MPS IVA. 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 240 weeks (Figure 2).

FIGURE 2: STUDY DESIGN OF THE MOR-004 CORE STUDY AND THE MOR-005 EXTENSION STUDY

qow = every other week; wk = week.

In the initial submission, the manufacturer provided the results of MOR-005 up to January 4, 2013. This included data from Part 1 (i.e., the 24-week blinded follow-up of MOR-004), representing a total follow-up of 48 weeks from MOR-004 baseline. Results for MOR-005 are provided in terms of week 24, 36, and 48 from MOR-004 baseline, which coincide with weeks 0, 12, and 24 of MOR-005 Part 1 (Table 4).

TABLE 4: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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6MWT = six-minute walk test; 3MST = three-minute stair-climb test; FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second; MVV = maximum voluntary ventilation.
* From MOR-004 baseline. Week 24 results represent means for patients who eventually completed the week 48 assessment. Therefore, these results may differ from the MOR-004 end point results.

In this resubmission, the manufacturer included week 120 results from the MOR-005 Part 2. Analyses of the new data were conducted in both the intention-to-treat (ITT) and modified per-protocol (MPP) populations. The ITT population consisted of patients who were previously included in the MOR-004 study and received at least one dose of ESA. The MPP population excluded patients who had undergone orthopedic surgery within 120 weeks or had missed 20% or more of the scheduled infusions. The submitted data did not provide details on the differences between the included patients in the ITT and MPP sets.

a) Results of the six-minute walk test at week 120

Patients treated with ESA continued to show improvement in 6MWT distance up to 72 weeks of treatment; after this time point, the 6MWT seemed to decline to values approaching those at baseline of MOR005 (Figure 3). [redacted]

[redacted].

FIGURE 3: [redacted]

The manufacturer compared patients in MOR-004/005 with untreated patients from the MOR-001 study (MorCAP study). The comparison was based on ANCOVA (analysis of covariance) analysis of the difference in change from baseline in 6MWT between treated and untreated patients (Figure 3). The manufacturer reported that the difference in the 6MWT between MOR-005 and MorCAP was statistically significant regardless of the population evaluated ([redacted]). This comparison is limited by the use of two different populations to evaluate the efficacy of an intervention; the different times in which the studies were conducted; the fact that the intervention was not randomized to the two populations; and the fact that the various baseline confounders could not be controlled through randomization. Given the limitations in the knowledge of this condition and uncertainties associated with the outcomes being measured, the effect of unknown and unmeasured confounders could be very pronounced. Therefore, this analysis should be considered exploratory, and should not be used to draw conclusions on the efficacy of ESA.

CDR noted that disease progression (6MWT decline rate) was similar for MorCAP, ITT, and PP populations after 72 weeks of treatment (Figure 3). However, it should also be noted that these data have significant limitations, as stated previously, and this should be considered hypothesis-generating only.

The manufacturer stratified 6MWT results based on baseline severity defined by 6MWT distance (200 m cut-off in Figure 4) and the use of walking aids at baseline (Figure 5). Based on general trends observed in the submitted Figure 4, Figure 5, and Figure 6, [redacted], leading these observations to be hypothesis-generating only.

FIGURE 4: [redacted]

FIGURE 5: [redacted]

The manufacturer showed that patients who were treated for the longest time period (2 mg/kg/week for 120 weeks) demonstrated the greatest sustained improvement over the 120 weeks' duration (Figure 6).

FIGURE 6: [redacted]

b) Results of pulmonary function at week 120

The manufacturer reported that respiratory function tests included MVV, FVC, FEV_1, and forced inspiratory vital capacity (FIVC). However, the manufacturer reported FVC and MVV results only.

The improvements in FVC observed at week 24 were further improved by a mean (SE) increase of 0.08 (0.02) L and 0.09 (0.02) L (or 8.6% and 8.9%) by week 120 for the ITT and MPP populations, respectively (Figure 7). The FVC improvement in absolute and percentage change from baseline was similar for the ITT and the MPP populations; however, the improvements are non-statistically significant.

FIGURE 7: [redacted]

[redacted]

FIGURE 8: [redacted]

4.2.4 Efficacy and safety of elosulfase alfa in patients younger than five years

At the initial submission, CDEC noted that there was no evidence on the efficacy and safety of ESA in pediatric patients younger than five years. The manufacturer provided results from MOR-007 to address CDEC's concerns.

The MOR-007 clinical trial is an open-label, single-group, multinational safety and efficacy study in patients with a documented clinical diagnosis of Morquio A who are younger than five years. Patients with a prior hematopoietic stem cell transplant or major surgery within three months of study entry or planned major surgery during the 52-week treatment period were not eligible to participate in MOR-007.

Eligible patients received weekly infusions of 2 mg/kg ESA for a total of 52 consecutive weeks. MOR-007 is ongoing. However, all patients enrolled in the study have completed the primary treatment phase (week 52).

The primary objective of the MOR-007 clinical trial is to evaluate the safety and tolerability of ESA 2 mg/kg/week after 52 weeks of treatment and long-term safety in an additional extension phase of 156 weeks. Safety will be assessed by examining the incidence, severity grade, and its relationship to the

study drug for all treatment-emergent adverse events (TEAEs) reported during the study period. In addition, secondary objectives are to assess changes in urine KS levels from baseline and to evaluate the impact of ESA on growth velocity over 52 weeks.

The 6MWT or 3MSCT are not included as efficacy outcomes in this trial, as these measures are not recommended for pediatric patients.

a) MOR-007 subject demographics

A total of 15 patients under the age of five have been enrolled in the MOR-007 study. All patients completed the primary treatment phase, and none permanently discontinued ESA. A summary of patient demographics is provided in Table 5.

The majority of patients enrolled in the study have abnormal musculoskeletal features (93.3%), with knee deformities (66.7%), pectus carinatum (66.7%), kyphosis (60.0%), and dysmorphism (60%). Other noted findings included abnormal general appearance (60.0%), abnormal head, eyes, ears, nose, and throat (66.7%), corneal opacity (clouding) (33.3%), and deafness (53.3%). Three patients have cardiovascular abnormalities, including mild to moderate mitral, pulmonary, and/or tricuspid valve regurgitation and mitral and/or aortic valve thickening. In patients aged two years and older, standing height is severely affected, with nearly half of patients (46.7%) below the third percentile of normal for this age group.

TABLE 5: SUMMARY OF CHARACTERISTICS OF PARTICIPANTS IN MOR-007

	VIMIZIM 2.0 mg/kg weekly (n=15)
Age at enrollment (years)	
Mean (SD)	3.1 (1.3)
Median	3.1
Min, Max	0.8, 4.9
Age group (years), N (%)	
0 to < 3 years	7 (46.7)
≥ 3 to < 5 years	8 (53.3)
Sex, N (%)	
Female	8 (53.3)
Male	7 (46.7)
Race, N (%)	
Asian	4 (26.7)
White	10 (66.7)
Other: East Asian/African American	1 (6.7)
Ethnicity, N (%)	
Hispanic or Latino	1 (6.7)
Not Hispanic or Latino	14 (93.3)
Normalized uKS[a] (ug/mg)	
Mean (SD)	35.9 (12.3)
Median	35.4
Min, Max	18.8, 56.5
Length (cm)	
Mean (SD)	90.1 (9.3)
Median	89.6
Min, Max	75.8, 113.0
Standing height[b] (cm)	
Mean (SD)	88.9 (9.0)
Median	90.0
Min, Max	72.3, 109.2

KS = keratan sulfate; SD = standard deviation.

[a] Normalized urine KS is calculated as urine KS divided by urine creatinine. Mean normalized urine KS level in healthy controls aged 0.5 to 5 years is 0.24 (SD: 0.14) mcg/mg creatinine.

[b] Height was not obtained for 2 of the patients who were younger than 2 years.

b) Summary of adverse events

The safety population consists of all patients who received any amount of ESA in study MOR-007. All of the patients have reported at least one AE; among them, 40% were classified as grade 1, which corresponds with mild severity, while 53.3% were classified as grade 2, which corresponds with moderate severity. Thirteen patients (87%) reported drug-related AEs, with pyrexia (53%) being the most commonly reported drug-related AE, followed by vomiting (40%) and abdominal pain (27%).

Overall, seven patients reported 21 SAEs. The SAEs reported included spinal cord edema and joint instability, hypersensitivity, sepsis, skin infection, device-related infection, tonsillar hypertrophy, and cervical cord suppression. Two SAEs in one patient were reported as drug-related by the investigator. No patients discontinued treatment due to AEs and there were no reported deaths.

c) Secondary outcomes

Secondary efficacy end points included levels of urine KS and growth velocity.

The mean height in patients aged two years or older increased by 5.3 (± 2.1) cm from baseline to week 52, which further increased to 7.6 (± 1.9) by week 104. After 52 weeks of treatment, cumulative growth rate remained positive for patients aged two years and older. The mean height z score for all patients was –2.0 (± 1.5) at baseline and –3.5 (± 0.8) after 104 weeks of treatment (Figure 9).

FIGURE 9: HEIGHT Z SCORE FOR PEDIATRIC PATIENTS TREATED WITH ELOSULFASE ALFA OVER 104 WEEKS

4.2.5 Patient selection and discontinuation criteria

In the original submission, there was insufficient evidence to identify the clinical characteristics of patients who are likely to achieve clinical benefit with ESA. Furthermore, CDEC was unable to identify reasonable discontinuation criteria for patients with MPS IVA who fail to respond to treatment with ESA based on the available evidence or clinical expertise.

The resubmission materials did not include evidence-based information to respond to CDEC concerns about patient selection or discontinuation criteria. Instead, the manufacturer included an opinion statements document authored by eight Canadian clinicians specializing in pediatrics, genetics, or metabolic disorders. It was reported that the clinical heterogeneity of Morquio A syndrome, compounded with the variable time point in the disease natural history when individual patients are diagnosed, warrants that the use of ESA in individual patients should be paired with personalized, measurable (every six months), clinically significant treatment goals. Treatment goals should take into consideration the burden of disease at the time of treatment initiation and the anticipated benefits over a defined period of time. The document also included that discontinuation of ESA should be considered if treatment goals are not reached, or if the patient does not comply with infusions or clinical monitoring of treatment goals.[3]

5. DISCUSSION

In the initial submission, CDEC issued a "do not list" recommendation for ESA. The main rationale for the recommendation included uncertain clinical relevance for improvement in 6MWT distance and failure to improve other clinical end points, including pain reduction, fatigue, disease progression, or the need for surgical intervention. In this resubmission, there were no new clinical studies that met the inclusion criteria; however, the manufacturer provided new clinical data based mainly [redacted], ad-hoc responder analyses based on MOR-004, and long-term (120 weeks) results in terms of endurance and pulmonary function from the MOR-005 extension trial. Furthermore, the manufacturer included efficacy results in patients less than five years from MOR-007 after 52 weeks of treatment.

5.1 Overall elosulfase alfa efficacy

In the initial submission, ESA failed to show a statistically significant difference compared with placebo in any of the evaluated outcomes except for 6MWT. However, CDEC concluded that the clinical relevance of the difference in 6MWT between ESA and placebo was uncertain because there was no validated MCID for the 6MWT in MPS IVA patients. [redacted]. Hendriksz et al.[12] reported multi-domain responder analysis using MOR-004 results; Hendriksz's MCID for 6MWT was based on a post-hoc Delphi consensus panel, which reported an MCID of 15%.[13]

The manufacturer reported long-term (up to 120 weeks) efficacy data from the extension study MOR-005. Patients treated with ESA continued to show improvement in 6MWT distance up to 72 weeks of treatment; after this time point, the 6MWT seemed to decline back to values approaching those at baseline of MOR-005. Similarly, improvement in FVC reported at the end of MOR-004 continued to improve; however, the improvements were non-statistically significant.

Safety and efficacy of ESA were reported for 15 pediatric patients younger than five years included in MOR-007. Results at 52 weeks showed that no patients discontinued treatment due to AEs and there were no reported deaths. Growth velocity was used as an efficacy outcome in MOR-007, and the results showed that ESA might have a positive effect on growth, but the relative efficacy compared with placebo or no treatment is not known.

5.2 Potential place in therapy

Currently, all therapies for MPS IVA are in essence reactive, focused on treating complications of the disease. This is an ongoing process, as MPS IVA is progressive disorder and current treatments do not address the underlying pathogenic process. ESA is a recombinant form of the missing enzyme, and is the only available therapy to address the lack of a functioning enzyme and potentially reduce or reverse the disease process caused by the accumulation of keratan and chondroitin sulfate. Like other approved enzyme replacement therapies, the challenge is that this drug is delivered externally and not endogenously produced intracellularly. While there are limitations to the strategy, it is currently the only alternative. Despite the limitations of the pivotal trials, enzyme replacement therapy for MPS types I, II, and VI has become the standard of care for those conditions. It is expected that ESA will fill a similar role for MPS IVA and also stimulate a better understanding of the condition and ongoing development of other specific therapies that may enhance its effectiveness.

Like other similar genetic conditions, a number of pre-existing factors will affect the response to therapy. These include the nature of the underlying DNA mutation, the age of the patient starting therapy, and the impact of pre-treatment allied therapies, such as surgery for mobility. All of these factors need to be taken into account prior to starting treatment.

These factors, along with completing baseline testing, would inform the decision to treat and be used to monitor treatment response. The majority of these tests will be similar to established tests that are undertaken in clinical trials and for which is a lot of experience, but it is expected that other, more specific, validated testing to assess endurance, pulmonary function, and HRQoL may be used in the future as research evolves. Because of the specific nature of these assessments, only specialist centres with adequate experience should initiate treatment, with ongoing central support and funding to complete clinical tests and DNA testing. It is reasonable that all patients should be offered a trial for at least 12 to 18 months, unless there is clear evidence that the severity of disease has reached a critical point, or there are other factors present that would mean this treatment is unlikely to have any impact.

A predefined managed access program similar to that published by the National Institute for Health and Care Excellence/National Health Service (England) could serve as a model. Prior to starting such a trial, there should be a clearly documented plan of the goals of therapy such that all parties are clear on what the aims are in terms of disease reversal or stability which, if not reached, would lead to stopping therapy. Due to the heterogeneity associated with this condition, for the reasons outlined previously, it is often difficult to predict the response to treatment.

6. CONCLUSIONS

Key concerns regarding the initial submission were uncertainty of the clinical relevance for improvement in 6MWT distance and failure to improve other clinical end points, including pain reduction, fatigue, disease progression, or the need for surgical intervention. Other concerns included limited evidence on long-term safety and efficacy, efficacy and safety in pediatric patients younger than five years, and criteria for patient selection and treatment stopping. The resubmission consisted mainly of [redacted], ad-hoc responder analyses based on MOR-004, and long-term (120 weeks) results in terms of endurance and pulmonary function from the MOR-005 extension trial.

No new clinical evidence met the inclusion criteria of the original systematic review. [redacted]; however, this is likely an underestimate, [redacted] closer to that reported in existing literature. The long-term efficacy data from the extension study MOR-005 showed that improvement in 6MWT and FVC continued up to 72 weeks of treatment; however, 6MWT results at 120 weeks appeared to decline to baseline values. No additional safety signals were identified for pediatric patients younger than five years in MOR-007.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups. The patient groups have requested that the summary of the first Vimizim submission by CADTH staff be used in this section.

1. Brief description of patient groups supplying input

Two patient groups provided a joint submission: the Isaac Foundation for MPS Treatment and Research, whose mission is to fund innovative research projects that aim to find a cure for MPS and to provide support for and advocate on behalf of families of individuals suffering from MPS; and the Canadian Society for Mucopolysaccharide and Related Diseases Inc. (the Canadian MPS Society), which is committed to providing support to individuals and families affected by MPS and related diseases, educating medical professionals and the general public about MPS, and raising funds for research.

The Isaac Foundation received sponsorship funding for various events from BioMarin Pharmaceutical Inc., Shire Pharmaceuticals Ltd., and Janssen Pharmaceuticals, Inc. The Canadian Society for Mucopolysaccharide and Related Diseases receives unrestricted grants and events sponsorships from Genzyme Canada, Shire Pharmaceuticals Ltd., and BioMarin Pharmaceutical Inc.

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.

Given the progressive nature of the disease and the range of sequelae of the enzyme deficiency, MPS IVA has a profound impact on all parts of a patient's life. It 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 (QoL). 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 QoL. Patients may initially be able to do daily activities such as biking, skating, walking, dressing themselves, and grocery shopping, but as the condition progresses, patients are increasingly reliant on caregivers and mobility aids. Patients report difficulty with self-care (due to difficulty reaching the backs 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/or 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 Syndrome. Those surveyed reported financial, emotional, and relationship stress. Some of the financial stress comes from costly home renovations and costly devices. Patients 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 with 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 previously, 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 orthopedic surgery — in some cases up to six previous surgeries — including knee stapling, hip replacement, spinal fusion, and spinal cord decompression. The subsequent post-surgical care can pose a burden to patients and caregivers, as significant pain, reduced mobility, and prolonged recovery times can 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' QoL. 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 benefits. They are willing to spend a day a week receiving infusion therapy, realizing that if the disease stabilizes with treatment, it could mean spending less time undergoing other procedures in the future. It is anticipated that improvements in the condition will lead to fewer procedures and reduced 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. Improved respiratory symptoms and reduced ear and upper respiratory infections were also noted. 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:	December 10 2015
Alerts:	Weekly search updates until April 20 2106
Study Types:	No search filters were applied
Limits:	No date or language limits were used

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
1. (vimizim* or elosulfase* or rhgalns or bmn-110-504 or bmn110 or bmn-110 or ODJ69JZG85).ti,ab,ot,rn,hw,nm,kf. 2. (enzyme* or recombinant).ti,hw,kf. 3. ((mucopolysaccharidosis* adj3 (iv or iva)) or mpsiv or mps-iv or galns* or morquio* or n-acetylgalactosamine-6-sulfat* or galactose-6-sulfat*).ti,hw,kf. 4. 2 and 3 5. galns protein, human.nm. 6. 9025-60-9.rn,nm. 7. 1 or 4 or 5 or 6 8. 7 use pmez 9. *elosulfase alfa/ 10. (vimizim* or elosulfase* or rhgalns or bmn-110-504 or bmn110 or bmn-110).ti,ab. 11. (enzyme* or recombinant).ti,kw. 12. ((mucopolysaccharidosis* adj3 (iv or iva)) or mpsiv or mps-iv or galns* or morquio* or n-acetylgalactosamine-6-sulfat* or galactose-6-sulfat*).ti,kw. 13. 9 or 10 14. 11 and 12 15. 13 or 14 16. 15 use oemezd 17. 8 or 16 18. 17 not conference abstract.pt. 19. exp animals/ 20. exp animal experimentation/ or exp animal experiment/ 21. exp models animal/ 22. nonhuman/ 23. exp vertebrate/ or exp vertebrates/ 24. animal.po. 25. or/19-24 26. exp humans/ 27. exp human experimentation/ or exp human experiment/ 28. human.po. 29. or/26-28 30. 25 not 29 31. 18 not 30

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	December 7 2015
Keywords:	Elosufase alfa, mucopolysaccharidosis iv
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* (https://www.cadth.ca/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: LIST OF EXCLUDED STUDIES

Excluded studies	Reason of exclusion
MOR-004[17]	Included in the initial submission
US Food and Drug Administration. Statistical review(s). In: Vimizim (elosulfase alfa)[18]	
US Food and Drug Administration. Medical review(s). In: Vimizim (elosulfase alfa)[19]	
Hendriksz et al., 2014[20]	
Hendriksz et al., 2014[10]	
MOR-005[21]	Not design of interest: open-label extension
MOR-007[22]	Not design of interest: open-label, single-group

APPENDIX 4: SUMMARY OF THE ORIGINAL SUBMISSION

Aim

To describe the characteristics and main results of the clinical trials included in the previous review by the CADTH Common Drug Review (CDR).

Description of studies

A total of one study was identified from the literature for inclusion in the previous systematic review: MOR-004 was a 24-week, multi-centre, multinational (17-country), three-group, double-blind, randomized (1:1:1), placebo-controlled trial of 177 patients with mucopolysaccharidosis type IVA (MPS IVA, also known as Morquio A syndrome), with randomization stratified by age and screening six-minute walk test (6MWT). The primary objective of the trial was to test the efficacy and safety of two regimens of elosulfase alfa (ESA) compared with placebo in patients with a clinical diagnosis of MPS IVA.

TABLE 6: DETAILS OF STUDIES INCLUDED IN THE CDR REVIEW

		MOR-004
DESIGNS & POPULATIONS	**Study Design**	24-week, multinational, DB, placebo-controlled, parallel-group (1:1:1) RCT. Randomization stratified by age and screening 6MWT.
	Locations	33 study centres in 17 countries: Canada, USA, W. Europe, S. 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
	Comparator(s)	Matching placebo
	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

		MOR-004
NOTES	**Publications**	Hendriksz et al. (2014)[10]

3MSCT = three-second stair-climb test; 6MWT = six-minute walk test; CDR = CADTH Common Drug Review; DB = double-blind; ESA = elosulfase alfa; IV = intravenous; KS = keratan sulfate; MPS IVA = mucopolysaccharidosis type IVA; MPS HAQ = Mucopolysaccharidosis type IVA Health Assessment Questionnaire; MVV = maximum voluntary ventilation; OLE = open-label extension (trial); PFT = pulmonary function test; RCT = randomized controlled trial; SCT = stem cell transplantation.

Population

The study population consisted of patients with a clinical diagnosis of MPS IVA who were at least five years of age without a history of surgical intervention in the three months preceding enrolment, and who 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. 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 on sex, with females accounting for 55% of the total. White patients made up 68% of the trial population, but with fewer white patients in the ESA group than in the placebo group (62.1% versus 74.6%). 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%).

TABLE 7: 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 (%)		
White	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[b]	30 (51.7)	22 (37.3)
Walking aid[c]	17 (29.3)	18 (30.5)

Characteristic	ESA Once-Weekly (n = 58)	Placebo (n = 59)
Weight (kg)		
Mean (SD)	22.9 (10.5)[d]	25.4 (11.5)
Median (range)	19.1 (12.0, 68.5)	23.0 (12.6, 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
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 or walking frame	7 (12.1)	6 (10.2)
Cane or walking stick	1 (1.7)	1 (1.7)
3MSCT (stairs/minute)		
Mean (SD)	29.6 (16.4)	30.0 (14.1)
Median (range)		
[redacted]		

ESA = elosulfase alfa; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; KS = keratan sulfate; MPS IVA = mucopolysaccharidosis type IVA; MVV = maximum voluntary ventilation; NR = not reported; SD = standard deviation.

Intervention
Patients were assigned 1:1:1 to ESA 2.0 mg/kg given by intravenous (IV) infusion either weekly or every other week, or matching placebo for a total of 24 weeks.

Outcomes
Endurance was assessed by the 6MWT and three-minute stair-climb test (3MSCT) during MOR-004. The primary efficacy outcome in MOR-004 was the change from baseline in 6MWT after 24 weeks. No published minimal clinically important differences (MCIDs) for either the 6MWT or 3MSCT in MPS diseases were identified. Urine keratan sulfate (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 Health Assessment Questionnaire (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). Items 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. There are no published MCIDs for the MPS HAQ. Pulmonary function tests were examined as a tertiary outcome in MOR-004; no published MCIDs in MPS disease were identified.

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 (SD) 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.

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 groups), the (modified) ITT set (n = 176) consisted of 58 patients randomized to weekly ESA, 59 to alternate-weekly ESA, and 59 to placebo.

Exposure to study treatment
The mean (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.

Efficacy
6-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).

3-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).

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.

Urine keratan sulfate

The percentage 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%).

Harms

Adverse events

The overall frequency of adverse events (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 placebo, 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%).

Serious adverse events

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

Withdrawal due to adverse events

There were no withdrawals due to adverse events (WDAEs) reported during the trial.

Summary of critical appraisal

- 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 for 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 using the 6MWT in MPS IVA. Other issues include a documented learning effect and potential limitations that are specific to the use of 6MWT in children, although the potential for bias from these aspects may be low, since all treatment groups should be equally affected, on average, in an RCT. Despite these limitations, the FDA accepted the use of the 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, and so it is unclear how this cut 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 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 and clinical end points, such as the need for surgery or mobility aids (e.g., a 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.

Summary of discussion

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; 40.9]). Pre-specified subgroup analyses that were performed and were of interest to the systematic review — age, baseline 6MWT, and geographic region — were consistent directionally and supportive of the primary analysis for an effect of ESA treatment; 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 (QoL), and need for mobility aids. Nevertheless, the FDA accepted the 6MWT as an intermediate outcome for MPS IVA trials, 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.

Findings from the 3MSCT — another marker of endurance —as well as urine KS, key pulmonary function tests (i.e., forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], and maximum voluntary ventilation [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.

Patient input for this submission indicated that patients would be willing to tolerate “serious adverse events” in order to experience benefit from therapy. 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.

Conclusion

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 five years 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 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. Either results were not statistically significant or statistical comparisons were not made for other outcomes of interest to this review, including the 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 WDAEs or deaths reported during the trial. No additional safety signals were identified from the data in the open-label extension trial (MOR-005).

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