Common Drug Review
Clinical Review Report

November 2016

Drug	Galsulfase (Naglazyme)
Indication	Long-term ERT in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)
Reimbursement request	As per indication
Dosage form(s)	5 mg/5 mL (1 mg/mL) solution for intravenous infusion
NOC date	September 16, 2013
Manufacturer	BioMarin Pharmaceutical Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in inherited metabolic diseases who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

3MSCT	three-minute stair climb test
6MWT	six-minute walk test
12MWT	12-minute walk test
AE	adverse event
ASB	arylsulfatase B (*N*-acetylgalactosamine-4-sulfatase)
CDR	CADTH Common Drug Review
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ERT	enzyme replacement therapy
DB	double-blind
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GAG	glycosaminoglycan
HSCT	hematopoietic stem cell transplantation
MCID	minimal clinically important difference
MPS	mucopolysaccharidosis
MPS VI	mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)
QoL	quality of life
IAE	infusion-associated event
IAR	infusion-associated reaction
IV	intravenous
ROM	range of motion
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) (MPS VI) is a rare autosomal recessive genetic disorder. There are approximately 15 to 20 potential patients in Canada.[1] MPS VI is caused by deficient activity of arylsulfatase B (*N*-acetylgalactosamine-4-sulfatase) (ASB), which results in impaired degradation and consequent accumulation of the glycosaminoglycan (GAG) dermatan sulfate.[2] MPS VI is a clinically progressive disease with a spectrum of mild to severe clinical manifestations.[2] Patients usually appear normal at birth, followed by progressive clinical manifestations including short stature with coarse facial features, skeletal and joint abnormalities, spinal cord compression, and compromised pulmonary and cardiovascular function.[2-4] Many patients with MPS VI do not live to adulthood.[3] By their late teen to adult years, patients often require clinical interventions related to dysfunction of one or more organs, such as corneal transplants, cardiac valve replacement, hip replacement, or spinal cord decompression surgery.[5]

Internationally, guidelines for management of MPS VI recommend galsulfase, a recombinant form of ASB, as first-line therapy.[5,6] Supportive care for MPS VI consists of surgical procedures, medications for infections, pain, and cardiac failure, physical and occupational therapy for stiff joints, and positive airway pressure for sleep apnea. Hematopoietic stem cell transplantation is also sometimes considered to restore ASB activity.

Galsulfase is approved by Health Canada for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of MPS VI. The recommended dosage regimen of galsulfase is 1 mg per kg of body weight administered once weekly as an intravenous (IV) infusion. There is no evidence for special considerations when galsulfase is administered to the pediatric population; however, data from patients aged one year or younger are limited.[5,7]

The objective of this review is to evaluate the beneficial and harmful effects of galsulfase 1 mg/kg IV infusion once weekly as long-term ERT in patients with MPS VI.

Results and interpretation

Included studies

The evidence for this review was derived from one phase 3 (ASB-03-05), double-blind (DB), randomized, placebo-controlled study comprising 39 patients aged seven years or older with a confirmed diagnosis of MPS VI. Eighty-five per cent of patients were aged younger than 18 years, and despite the stated inclusion criteria, three patients between the ages of five years and seven years were enrolled in the trial. The clinical expert consulted for this review indicated that the condition of patients included in study ASB-03-05 was clinically moderate in severity. Patients were randomly assigned to either weekly galsulfase 1 mg/kg or a matching placebo solution weekly for 24 weeks. The groups were similar on most baseline characteristics; however, the mean baseline 12-minute walk test (12MWT) distance was higher in the placebo group compared with the galsulfase group. One patient discontinued the study prematurely (in the placebo group, due to withdrawal of consent). The primary efficacy outcome was 12MWT distance at 24 weeks, and secondary efficacy outcomes included the three-minute stair climb test (3MSCT) and urine GAG levels. No studies validating these outcomes or reporting minimal clinically important differences (MCIDs) in patients with MPS VI were identified, which makes it challenging to interpret the clinical relevance of the findings. The study was not designed to assess outcomes of direct importance to patients such as survival, disease progression, and quality of life (QoL). Other key

limitations of the study were lack of reporting on use of clinically important concomitant medication such as analgesics that could have affected the primary efficacy outcome; the lack of data for patients younger than five years of age, in light of comments from the clinical expert consulted for this review indicating that ERT may be initiated in younger children in clinical practice; and the limited data (from only six patients) for adults with MPS VI.

Efficacy and safety data from ASB-03-06, the open-label extension study of ASB-03-05 in which all patients completing ASB-03-05 were treated with galsulfase 1 mg/kg weekly, were also available.

Efficacy

A statistically significant increase in 12MWT was observed from baseline to week 24 favouring galsulfase (adjusted mean difference at 24 weeks: 92 m, 95% confidence interval [CI], 11 m to 172 m, $P = 0.025$). Data from various pre-specified subgroup and sensitivity analyses were directionally consistent and supportive of the primary analysis. Urine GAG levels were statistically significantly lower in the galsulfase group compared with placebo at week 24 (mean –227 mcg/mg creatinine, 95% CI, –265 to –190 mcg/mg creatinine, $P < 0.001$). Findings from 3MSCT, height, pulmonary function (i.e., forced vital capacity [FVC]; forced expiratory volume in one second [FEV_1]), and shoulder range of motion were either statistically non-significant or were not compared between treatments. Data on clinically important outcomes such as survival, progression to wheelchair dependence, surgeries (e.g., corrective orthopaedic), cardiac or respiratory failure, QoL, and health resource utilization were either not reported or reported descriptively and were largely uninformative.

Efficacy data were available for week 96 after ASB-03-05 baseline from the open-label extension study (ASB-03-06). The observed increases in 12MWT in the galsulfase group of the randomized controlled trial (RCT) appeared to be maintained in the extension study, and patients in the placebo group switched to galsulfase in the extension study made gains in 12MWT walking distance.

Harms

Overall, adverse events (AEs) in ASB-03-05 were common in both treatment groups. All patients experienced at least one AE during the 24-week study. The most common AEs in galsulfase-treated patients, which also appeared to occur at a higher frequency (> 2%) than in the placebo group, were [redacted] Numerically, more serious adverse events (SAEs) occurred in patients treated with placebo (12 SAEs) compared with galsulfase (three SAEs). [redacted] All patients except one in the placebo group completed the study. Eleven patients in the galsulfase group and eight in the placebo group experienced infusion-associated events (IAEs). There were no withdrawals due to adverse events (WDAEs) and no deaths reported during the trial.

[redacted] The clinical expert consulted for this review indicated that antibodies against galsulfase may not be neutralizing antibodies; therefore, the therapeutic efficacy of galsulfase may not be affected by the presence of antibodies.

Conclusions

In a single RCT (ASB-03-05) of 39 patients, galsulfase IV infusion once weekly was shown to improve 12MWT distance compared with placebo in patients seven years of age and older with a confirmed diagnosis of MPS VI, most of whom were adolescents and pre-adolescents. There were no data reported for outcomes of direct relevance to patients, such as disease progression, QoL, or survival. Although 12MWT is accepted by regulatory authorities as an outcome in MPS VI, the clinical importance of the observed improvement is unclear in the absence of studies validating this outcome in patients with MPS VI. Therefore, it is unclear whether the findings for 12MWT will translate to improved survival, disease stabilization, reduced need for surgical intervention, or improved QoL. Results were either not statistically significant or statistical comparisons were not made for other outcomes of interest to this review, including the 3MSCT, height, and shoulder range of movement. Galsulfase treatment was more commonly associated with pyrexia, abdominal pain, [redacted] and rash versus placebo. Numerically, more SAEs occurred in the placebo group than in the galsulfase group. No WDAEs or deaths were reported during the study. No additional safety signals were identified in the open-label extension trial at three years after ASB-03-05 baseline.

TABLE 1: SUMMARY OF RESULTS

	ASB-03-05	
Outcomes	**Galsulfase (N = 19)**	**Placebo (N = 20)**
12MWT (m)		
Baseline	227 ±1 70	381 ± 202
Change from baseline at week 24, mean (SD)	109 ± 154	26 ± 122
Adjusted mean difference at week 24, mean (95% CI)[a]	92 (11 to 172)	
P value	0.025	
3MSCT (stairs/min)		
Baseline	19.4 ± 12.9	31.0 ± 18.1
Change from baseline at week 24, mean (SD)	7.4 ± 9.9	2.7 ± 6.9[b]
Adjusted mean difference at week 24, mean (95% CI)	5.7 (–0.1 to 11.5)	
P value	0.053	
Withdrawals, n (%)	0	1 (5)
≥ 1 SAE, n (%)	3 (16)	4 (20)
Number of SAEs	3	12
WDAE, n (%)	0	0
Notable harms(s), n/N (%)		
Patients with IAR	11 (58)	8 (40)
Patients with IAR during infusion	10 (53)	4 (20)

3MSCT = three-minute stair climb test; 12MWT = 12-minute walk test; CI = confidence interval; IAR = infusion-associated reaction; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.
[a] Adjusted for baseline 12MWT.
[b] Included 19 patients because one patient discontinued the study at week 5.
[c.] Adjusted for baseline 3MSCT.

1. INTRODUCTION

1.1 Disease prevalence and incidence

Mucopolysaccharidosis VI (MPS VI, also known as Maroteaux-Lamy syndrome) is a rare, autosomal recessive lysosomal storage disorder. There are approximately 15 to 20 patients in Canada.[1] Mucopolysaccharidosis (MPS) is caused by reduced activity of the enzyme arylsulfatase B (*N*-acetyl-galactosamine-4-sulfatase) (ASB) due to mutations in the ASB gene. ASB hydrolyzes the sulfate moiety of the glycosaminoglycan (GAG) dermatan sulfate.[2] Patients with clinical manifestations of MPS VI generally have ASB enzyme activity level of less than 10% compared with controls. MPS VI is a clinically progressive disease with a spectrum of mild to severe clinical manifestations.[2] Rapidly progressing patients usually begin to show symptoms shortly after birth and are typically diagnosed between two and four years of age in the absence of a family history.[3] Patients usually appear normal at birth, but intracellular GAG accumulation leads to progressive development of multiple clinical manifestations, including short stature with coarse facial features, skeletal abnormalities, spinal cord compression, compromised pulmonary and cardiovascular function, corneal clouding, and recurrent respiratory and ear infections.[2-4] Most do not live to adulthood.[3] Although symptoms may appear later in life in those with slowly progressing disease, these patients generally demonstrate severe morbidity and premature mortality by the third to fifth decade of life.[5]

MPS VI is usually suspected in a child with coarse facial features, hepatosplenomegaly, and bone disease, with or without central nervous system (CNS) abnormalities. However, the initial presentation may be subtle and signs may be variable, frequently resulting in delayed diagnosis. A comprehensive biochemical evaluation, such as urinary GAG level, may be needed for patients who present early in the course of disease. Urinary GAG levels of greater than 200 mcg/mg creatinine are generally associated with rapidly progressive disease, while urinary GAG levels of less than 100 mcg/mg creatinine are associated with a slowly progressing clinical course and longer survival. However, urinary GAG levels are not considered diagnostic on their own.[8] Definitive diagnosis requires assay of ASB enzyme activity (with concurrent measurement of other sulfatases)[8] using an approved method of enzyme testing, usually in peripheral blood leukocytes.[2] Enzyme testing may also be combined with genetic testing, or the latter may be used alone when there is a known mutation in a family that is associated with severe disease.

Patients with MPS VI typically present with radiological evidence of dysostosis multiplex, comprising malformations of the skull, thorax, spine, pelvis, long bones, and hands.[3] Patients with MPS VI usually do not exhibit neurocognitive deficits; however, physical limitations, particularly decreased hearing and vision, can affect learning and development.[3] The main clinical manifestations include bone and joint disease (leading to pain, disability, and wheelchair dependency), pulmonary insufficiency (leading to assistive and, in some cases, invasive ventilation), and cardiac disease (usually due to valvular insufficiency), with the latter two often contributing to early mortality. Input from patient groups indicated that MPS VI is a disease with numerous life-altering, life-threatening, and progressive symptoms. The impact of MPS VI on the musculoskeletal system was consistently described as associated with significant pain, loss of function, and reduced quality of life (QoL). Progressive loss of function from the disease resulted in an impaired ability to perform enjoyable activities such as playing team sports, playing musical instruments, and writing or drawing (see APPENDIX 1: PATIENT INPUT SUMMARY).

1.2 Standards of therapy

No Canadian or US clinical practice guidelines for the management of MPS VI were identified from the literature. Internationally, guidelines for management of MPS VI recommend galsulfase enzyme replacement therapy (ERT) as first-line therapy.[5,6] Supportive care for MPS VI consists of medical and surgical interventions aimed at symptom management, mitigating the debilitating manifestations and complications of the disease, and improving or maintaining QoL. A multidisciplinary team is typically involved in the care of patients with MPS VI, reflective of the multiple organ systems affected by the disease.[2,4,7,9] Patients often require clinical interventions such as corneal transplant, cardiac valve replacement, hip replacement, or spinal cord decompression surgery.[5] According to the clinical expert consulted by the CADTH Common Drug Review (CDR), the most common adjunctive pharmacotherapies used for symptom control include analgesics. Antibiotics may be required for treating acute respiratory infections, and medications may be used to manage cardiac and respiratory complications. Other supportive modalities include physical therapy for stiff joints and positive airway pressure for sleep apnea.

Another treatment option for MPS VI is hematopoietic stem cell transplantation (HSCT). This procedure is not frequently used, as it may be associated with substantial morbidity and mortality. However, the clinical expert consulted by CDR indicated that HSCT may be associated with more improved outcomes in the current clinical context than are reflected by the historical cases documented in the literature.[10]

1.3 Drug

Galsulfase is a recombinant form of human ASB intended to provide exogenous enzymes that can be taken up into lysosomes to increase the catabolism of GAG. Galsulfase is indicated for long-term ERT in patients with a confirmed diagnosis of MPS VI. The recommended dosage of galsulfase is 1 mg per kg of body weight administered once weekly as an intravenous infusion over a period of no less than four hours. The rate of infusion can be adjusted depending on body weight. The product monograph specifies that there is no evidence for special considerations when galsulfase is administered to pediatric patients; however, it highlights that data are limited for patients aged one year or younger.[5,7]

Indication under review
Long-term ERT in patients with a confirmed diagnosis of MPS VI (Maroteaux-Lamy syndrome)
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 galsulfase (1 mg/kg of body weight intravenous [IV] infusion, once weekly) for long-term ERT in patients with a confirmed diagnosis of MPS VI.

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 VI Subgroups: • Age (< 1 year vs. ≥ 1 year, < 18 years vs. ≥ 18 years) • Endurance and mobility (e.g., baseline 6MWT or 12MWT; use of wheelchairs or walking aids) • Presence or absence of cardiac failure • Presence or absence of tracheostomy
Intervention	Galsulfase 1 mg/kg body weight IV once weekly
Comparators	Best supportive care Placebo
Outcomes	**Efficacy outcomes:** **Key outcomes** • Survival[a] • Disease progression[a] o Wheelchair/walking aid use o Surgeries (e.g., corrective orthopaedic procedures) o Cardiac failure o Respiratory failure • Endurance[a] o 6MWT or 12MWT o 3MSCT • Height and weight percentiles[a] **Other outcomes** • QoL (using validated questionnaire; e.g., SF-36, Health Assessment Questionnaire)[a] • Pulmonary function (e.g., FEV_1) • Skeletal/soft tissue (e.g., joint mobility, joint pain and stiffness questionnaire scores, grip and pinch strength, bone density)[a] • Health resource utilization (such as hospitalization, use of adjunctive treatments) • Sleep function (e.g., polysomnography) • Hearing function • Ophthalmological evaluation • Size of liver and spleen • Urinary glycosaminoglycans **Harms outcomes:** AEs, SAEs, WDAEs, mortality, serum anti-galsulfase antibody; notable harms (injection-related adverse events, tracheotomy)

Study Design	Published and unpublished phase 3 RCTs

3MSCT = three-minute stair climb test; 6MWT = six-minute walk test; 12MWT = 12-minute walk test; AE = adverse event; FEV_1 = forced expiratory volume in one second; IV = intravenous; MPS VI = mucopolysaccharidosis VI (Maroteaux-Lamy syndrome); RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short-Form 36-Item Health Survey; vs. = versus; WDAE = withdrawal due to adverse event.
[a] Outcomes considered important by patient group.

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 Naglazyme and galsulfase.

No methodological filters were applied to limit 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, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 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 Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Clinical Trials; 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. 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 study is summarized in Table 3 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

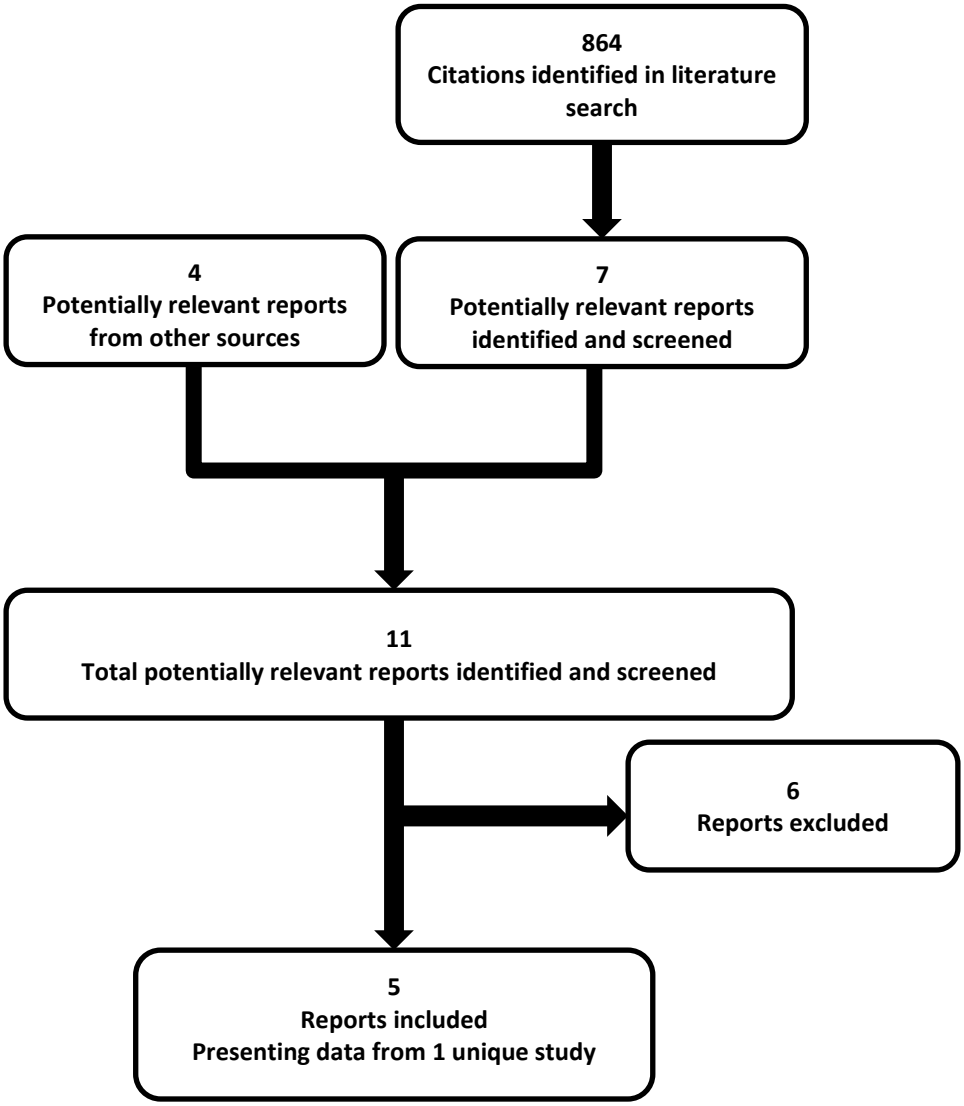

TABLE 3: DETAILS OF INCLUDED STUDIES

		ASB-03-05
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	US, Germany, England, France, Brazil, and Portugal
	Randomized (N)	39
	Inclusion Criteria	• ≥ 7 years of age • Diagnosis of MPS VI, confirmed by clinical signs and symptoms of MPS VI, and a documented fibroblast or leukocyte ASB enzyme activity level of less than 10% of the lower limit of the normal range of the measuring laboratory • In the screening 12MWT, able to walk independently ≥ 5 metres and < 270 metres in the first 6 minutes, or < 400 metres total in 12 minutes
	Exclusion Criteria	• Pregnant or lactating • Serious intercurrent illness • Previously undergone HSCT (i.e., bone marrow or cord blood transplantation) or major organ transplantation • Clinically significant spinal cord compression • Known hypersensitivity to galsulfase or to components of the active or placebo test solutions • Previously received galsulfase
DRUGS	**Intervention**	1 mg/kg galsulfase, IV infusion, once weekly
	Comparator(s)	Placebo solution, IV infusion, once weekly
DURATION	**Phase**	
	Run-in	None
	DB	24 weeks
	Open-label phase	[redacted]
	Follow-up	None
OUTCOMES	**Primary End Point**	12MWT
	Other End Points	• Urinary GAG measurements • 3MSCT • Shoulder ROM • Coin pick-up test • Joint pain and stiffness, and physical energy level • Visual acuity[a]
NOTES	**Publications**	Harmatz et al. (2006)[11]

3MSCT = three-minute stair climb test; 12MWT = 12-minute walk test; ASB = arylsulfatase B (or N-acetylgalactosamine-4-sulfatase); DB = double-blind; GAG = glycosaminoglycan; HSCT = hematopoietic stem cell transplantation; IV = intravenous; MPS VI = mucopolysaccharidosis VI (Maroteaux-Lamy syndrome); RCT = randomized controlled trial; ROM = range of motion.

[a] No results on visual acuity were reported.

Note: 3 additional reports were included: Food and Drug Administration reports[12,13] and Health Canada review report.[14]

Source: Study ASB-03-05 Clinical Study Report.[15]

3.2 Included studies

3.2.1 Description of studies

ASB-03-05 was a 24-week, phase 3, randomized, double-blind (DB), placebo-controlled, multinational clinical study of the efficacy and safety of galsulfase in 39 patients with MPS VI. Eligible patients were randomized to either 1 mg/kg galsulfase or placebo solution (1:1 ratio) weekly for 24 consecutive weeks. Randomization was stratified by primary site of treatment. Within each site, randomized blocks governed allocation to treatment group. Patients, investigators, site personnel, and the sponsor's staff had no knowledge of treatment assignment. Among 39 included patients, six (15%) were from the US, 25 (64%) were from European countries, and eight (21%) were from Brazil. At the end of the randomized controlled trial (RCT), 38 patients entered a 240-week, open-label extension study (ASB-03-06),[16] in which all patients received galsulfase 1 mg/kg of body weight by IV weekly. The objective of this extension study was to assess the long-term efficacy and harms of galsulfase (APPENDIX 6).

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients at least seven years of age with a clinical diagnosis of MPS VI were included in study ASB-03-05.[15] The diagnosis of MPS VI was confirmed by low ASB enzyme activity level (less than 10% of the lower limit of the normal range of the measuring laboratory) in leukocyte or fibroblast cell lines. Fibroblast cell lines were also used to establish genotype.[15] At screening, patients had to be able to walk a distance ≥ 5 m and < 270 m on the six-minute walk test (6MWT) or < 400 m on the 12-minute walk test (12MWT). Patients with significant medical conditions, prior hematopoietic stem cell (i.e., bone marrow or cord blood transplantation) or major organ transplantation, clinically significant spinal cord compression, or prior treatment with galsulfase were excluded from the study. The clinical expert consulted by CDR on this review indicated that patients with MPS VI participating in study ASB -03-05 likely had disease of moderate clinical severity.

b) Baseline characteristics

The baseline characteristics of patients enrolled in ASB-03-05 are shown in Table 4. Eighty-five per cent of patients were younger than 18 years. Patients ranged in age from five to 29 years; the mean and median age in the galsulfase and placebo groups was 14 years and 11 years, and 12 years and 10 years, respectively. Three patients younger than the pre-specified age cut-off of seven years were included in the trial, as they met the walk test criteria and the investigators considered them mature enough to participate in the RCT; all three patients were randomized to the placebo arm. The majority (63% to 70%) were female. Mean standing height was similar between groups at approximately 100 cm. Body weight was also comparable in both groups. The baseline 12MWT was higher in the placebo group (mean ± standard deviation [SD]: 381 m ± 202) compared with the galsulfase group (227 m ± 170). Seven patients who did not meet the pre-specified walk test criteria were included in the study by expanding the original inclusion criteria from a 12MWT < 400 m to < 600 m; this was done because there were insufficient patients who met the original criteria. Clinical manifestations of MPS VI appeared similar in both groups (Table 4). Patients demonstrated a typical distribution of MPS VI signs and symptoms including coarsened facial features (100%); valvular disease (100%); musculoskeletal symptoms (100%); dysostosis multiplex (97%); sleep apnea (59%); pectus carinatum (77%); restrictive lung disease (69%); visual impairment (92%); hepatomegaly (87%); splenomegaly (79%); umbilical hernia (69%); and neurological symptoms (49%). Previous MPS VI-related surgery (87%) and MPS VI-related hospitalizations (41%) were also frequent.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	Galsulfase (N = 19)	Placebo (N = 20)
Age (years)		
Mean (SD)	13.7 (6.5)	10.7 (4.4)
Median	12	10
Range, n (%)	8 to 29	5 to 20
< 7 years	0	3 (15)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Sex, n (%)		
Female	12 (63)	14 (70)
Male	7 (37)	6 (30)
Race, n (%)		
Caucasian	16 (84)	15 (75)
Black	1 (5)	2 (10)
Other	2 (10)	3 (15)
Region, n (%)		
US	2 (11)	4 (20)
Europe	9 (48)	10 (50)
Brazil	4 (21)	4 (20)
12MWT (m), mean ± SD		
All patients, n (%)	19 (100)	20 (100)
Mean ± SD	227 ± 170	381 ± 202
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Pre-pubertal, n (%)	7 (37)	9 (45)
Mean ± SD	300 ± 193	361 ± 209
Pubertal, n (%)	5 (26)	7 (35)
Mean ± SD	252 ± 155	406 ± 211
Adult, n (%)	7 (37)	3 (15)
Mean ± SD	135± 132	334 ± 243
Standing height (cm)		
Mean ± SD	104.4 ± 12.87	100.3 ± 13.54
Range	90 to 136	81 to 140
Weight (kg)		
Mean ± SD	24.6 ± 9.14	20.8 ± 7.9
Range	14 to 47	14 to 46
MPS VI features, n (%)		
Coarse facial feature(s)	19 (100)	20 (100)
Macrocephaly	17 (89)	16 (80)
Macroglossia	17 (89)	19 (95)

Characteristics	Galsulfase (N = 19)	Placebo (N = 20)
Corneal clouding	19 (100)	19 (95)
Valve disease	19 (100)	20 (100)
Left heart failure	2 (11)	0
Sleep apnea	11 (58)	12 (60)
Pulmonary hypertension	4 (22)	3 (15)
Restrictive lung disease	14 (74)	13 (65)
Hepatomegaly	17 (89)	17 (85)
Splenomegaly	16 (84)	15 (75)
Joint stiffness	19 (100)	17 (85)
Joint pain	16 (84)	17 (85)
Cervical myelopathy	2 (11)	1 (5)
Communicating hydrocephalus	3 (16)	3 (15)
3MSCT (stairs/minute), mean ± SD		
All patients	19 (100)	20 (100)
Mean ± SD	19 ± 13	31 ± 18
Pre-pubertal, n (%)	7 (37)	9 (45)
Mean ± SD	24 ± 16	28 ± 19
Pubertal, n (%)	5 (26)	7 (35)
Mean ± SD	21 ± 12	34 ± 20
Adult, n (%)	7 (37)	4 (20)
Mean ± SD	14 ± 9	33 ± 16

3MSCT = three-minute stair climb test; 12MWT = 12-minute walk test; MPS VI = mucopolysaccharidosis VI (Maroteaux-Lamy syndrome); n = number of patients with event; N = number of patients; SD = standard deviation.
Note: Three patients were younger than 7 years old.
Source: Clinical Study Report p. 7 to 74, 164, 4143; Harmatz et al. (2006);[11] FDA report[12] p. 56, p. 70.

3.2.3 Interventions

Patients were assigned 1:1 to galsulfase 1 mg/kg body weight or placebo solution administrated by IV infusion weekly for a total of 24 weeks. The dose of galsulfase was recalculated at monthly intervals based on the most recent body weight. To maintain blinding, patients, parents, investigators, site personnel, and members of the sponsor's staff had no knowledge of treatment assignment. Adverse events (AEs) consistent with an infusion-associated reaction (IAR) — e.g., urticaria, shortness of breath, and tachycardia — were managed appropriately, such as by interrupting the infusion, decreasing the rate of infusion, or administering additional IV antihistamines, oxygen, IV fluids, or steroids. All medications taken by the patient beginning 30 days prior to enrolment through to the end of study participation were recorded. There were no medication restrictions during the course of the study, other than those regarding investigational medications.

3.2.4 Outcomes

The primary efficacy outcome in study ASB-03-05 was endurance measured by 12MWT. The supervised 12MWT test measures the distance a patient can walk on a hard, flat surface over a 12-minute period.[17] Walk tests aim to evaluate the global functioning of heart, lungs, peripheral circulation, blood, nervous system, muscles, bones, and joints.[17] Patients with MPS VI may have impaired walk distance due to numerous disease-related factors, including stunted growth, cardiac valve dysfunction, impaired lung function, and bone and joint deformities.[6] Although there are no studies validating the use of 6MWT or

12MWT in MPS diseases, regulatory authorities such as the FDA consider them to be acceptable surrogate measures for trials of MPS.[17] Minimal clinically important differences (MCIDs) for this outcome in other conditions such as chronic obstructive pulmonary disease (COPD) (43 metres) and heart failure (54 metres) may not be generalizable to patients with MPS VI, given key differences between these populations.[17,18] Patients with MPS VI are typically much younger than patients with COPD or heart failure, and have functional impairment primarily from musculoskeletal as well as cardiopulmonary causes.[17,18] (APPENDIX 5).

[redacted]

The secondary outcomes in study ASB-03-05 were the three-minute stair climb test (3MSCT) and urinary glycosaminoglycans (GAG). The 3MSCT is a test of global function that evaluates the number of steps climbed, allowing for use of handrails and rest periods, over three minutes.[18] The 3MSCT correlates strongly with other measures of endurance, such as 12MWT. However, no studies validating the 3MSCT in patients with MPS VI were identified. Due to the deficiency in ASB enzyme and the consequent accumulation of GAG, MPS VI is associated with a detectable rise in urinary GAGs, specifically, dermatan sulfate. Presence of elevated urine GAG is used to aid in the diagnosis of MPS VI and for monitoring disease activity. Urine GAGs are measured from the first morning void and normalized to urinary creatinine levels. No clear correlation has been reported between high urine GAG values (> 200 mcg/mg creatinine) and greater disease activity, as determined by shorter age-adjusted stature and body weight, endurance as measured by 6MWT, pulmonary function tests, or joint range of motion (ROM). Notably, urine GAG values can be falsely negative in patients with MPS VI with obvious sequelae of the disease.[6] No MCID was identified for urinary GAG in patients with MPS VI (APPENDIX 5).

Joint pain and stiffness, physical energy, shoulder ROM, and dexterity as measured by the coin pick-up test were identified as tertiary outcomes in ASB-03-05. Only descriptive analyses were reported for these outcomes. Cardiac and respiratory function, health resource utilization (antibiotic use, hospitalizations, days missed from school and work, requirement for wheelchair or other ambulatory aid, requirement for positive airway pressure during sleep) and visual function were assessed at baseline to provide additional documentation of the severity of the disease prior to treatment, and to allow for long-term evaluation of galsulfase treatment during the open-label extension study. However, the results for these outcomes were not reported for either the RCT (24 weeks)[15] or the extension study (72 weeks).[16]

Serious adverse events (SAEs), AEs, and infusion-associated AEs were reported. Safety was assessed by medical history, physical examinations, measurement of vital signs, signs and symptoms, and recording AEs.

3.2.5 Statistical analysis

The primary efficacy outcome was the 12MWT distance at week 24 adjusted for baseline 12MWT. Based on a previous phase 2 study, the estimated SD of the change in metres walked was approximately 150 m. The planned sample size of 18 in each treatment group was expected to yield approximately 80% power (two-sided P = 0.05) to detect a between-group difference in the primary outcome of 135 m. The method used for the analysis was a repeated measures linear model; the power with this approach was expected to be greater than 80% because it helps to reduce unexplained variability through repeated measures for each patient. The model was stratified by site and used baseline walk distance as a

continuous covariate. The missing post-baseline values for the patient who discontinued from the study at week 5 were imputed. The robustness of the primary efficacy analysis was explored through various sensitivity analyses involving different longitudinal models (see Appendix 4, Table 13 to Table 16) and adjustment for demographic characteristics or treatment sites.

The secondary efficacy analysis, of 3MSCT, was also based on a longitudinal repeated measures analysis adjusted for baseline 3MSCT. Urinary GAG levels at week 24 were compared between groups using an analysis of variance (ANOVA) model stratified by site with baseline urinary GAG level as a continuous covariate.

No statistical methods were employed to control for multiplicity of testing for the secondary and tertiary outcomes.

a) Analysis populations

Both efficacy and safety analyses included all randomized patients (intention-to-treat [ITT], n = 39). For the primary outcome (12MWT), three datasets were analyzed: all randomized; a walk-eligible subset that included patients satisfying the eligibility requirements with respect to their screening walk test results (< 270 m in 6MWT or < 400 m in 12MWT], n = 32); and patients with a 12MWT distance of ≤ 400 m at baseline (N = 28).

3.3 Patient disposition

Detailed information on patient disposition in study ASB-03-05 is presented in Table 5.
Only one patient (in the placebo group) discontinued from the study; the reason was withdrawal of consent.

TABLE 5: PATIENT DISPOSITION

	ASB-03-05	
	Galsulfase	Placebo
Screened, N	45	
Randomized, N (%)	19 (100)	20 (100)
Completed 24 weeks, N (%)	19 (100)	19 (95)
Discontinued, N (%)	0	1 (5)
Withdrew consent, N (%)	0	1 (5)
ITT, N (%)	[redacted]	[redacted]
PP, N	[redacted]	[redacted]
Safety, N (%)	[redacted]	[redacted]

ASB = arylsulfatase B (or N-acetylgalactosamine-4-sulfatase); ITT = intention-to-treat; N = total observed patients; NR = not reported; PP = per-protocol.
Source: Clinical Study Report p. 67, 409.

3.4 Exposure to study treatments

Detailed information on medication exposure is presented in Appendix 4 (Table 8).

[redacted]

3.5 Critical appraisal

3.5.1 Internal validity

Overall, methods for randomization and allocation concealment in study ASB-03-05 were appropriate. An interactive voice response system was used for treatment allocation. The mean age, height, body weight, and clinical MPS VI features and medical history appeared similar in both treatment groups. However, there was an imbalance in baseline 12MWT distance between treatment arms (227 ± 170 m and 381 ± 202 m in the galsulfase and placebo groups, respectively; see Table 4). There was also an imbalance in baseline 3MSCT (19.4 ± 12.9 and 31.0 ± 18.1 in the galsulfase and placebo groups, respectively). The between-group difference in baseline 12MWT distance was 154 metres (standard error [SE] 60). Given the small sample size of the trial, this imbalance may have been due to chance. It could also be due to the inclusion of three patients below the stated age threshold for eligibility of seven years in the placebo group, or seven patients who did not meet the stated eligibility criteria for walking distance. Regardless of the reason for the imbalance, the higher mean baseline 12MWT distance in the placebo group raises the possibility of a ceiling effect in this group — i.e., little further improvement may have been possible. This could have potentially biased the results for 12MWT in favour of galsulfase. However, the concern regarding a ceiling effect in the placebo group is mitigated somewhat by the finding in the extension phase that patients originally on placebo who were switched to active treatment after week 24 achieved a statistically significant improvement in 12MWT [redacted] (Appendix 4, Table 32).

A key limitation of the use of 12MWT as the primary outcome for the trial is that its validity in MPS VI diseases has not been studied. Other issues include a documented learning effect, and potential limitations that are specific to the use of 12MWT in children (APPENDIX 5). Despite these limitations, the FDA agreed to the use of 12MWT as an acceptable primary efficacy outcome for MPS VI in the ASB-03-05 study, on the basis that it was reflective of the functional limitations associated with the disease. However, the FDA did not consider 12MWT to be a surrogate for MPS VI-related morbidity or mortality.[12] Lack of validation is also a limitation of the other outcomes reported in ASB-03-05, namely 3MSCT and urinary GAG.

The clinical expert consulted for this review indicated that analgesics are often used by patients with MPS VI; as these medications reduce pain and may increase mobility and endurance, any imbalance between groups in their use could bias the 12MWT and 3MSCT results. The extent of analgesic use (e.g., dose and frequency) was not analyzed or clearly reported in ASB-03-05. Therefore, it is unclear whether the use of analgesics was balanced between treatment groups.

Finally, no statistical methods were employed to control for multiplicity (to control the type I error rate) in the analyses of the secondary and tertiary outcomes. This increases the risk of finding a statistically significant difference between groups due to chance.

3.5.2 External validity

According to the clinical expert consulted for this review, the patient population studied in ASB-03-05 was considered representative of patients with MPS VI seen in clinical practice in Canada. The overall mean age of patients in the trial was 12 years old (range: five years to 29 years), and the majority (> 85%) of patients were younger than 18 years of age. With only six patients older than 18 years of age, the findings of the study are likely most generalizable to the adolescent and pre-adolescent populations. Due to the limited lifespan of many patients with MPS VI, the age distribution in ASB-03-05 was thought to be consistent with the patient population encountered in clinical practice in Canada, according to the clinical expert consulted by CDR. Nevertheless, evidence for the use of galsulfase in adults is particularly

limited, which compromises generalizability to this population. The lack of data for children younger than seven years of age is also a limitation since the expert indicated that the drug was likely to be used in younger patients in clinical practice, and may indeed be more efficacious if started soon after diagnosis, before irreversible changes due to ASB deficiency are incurred.

Although there were no Canadian patients enrolled in this trial, six (15%) were from the US and 25 (64%) were from European countries. As clinical management is likely to be similar in these regions, generalization of the results to Canadian settings is not a major concern.

Patients were enrolled in the study if their screening 6MWT was between ≥ 5 m and < 270 m, and < 400 m on the 12MWT. This range was selected because it was thought that patients meeting this standard would have the greatest chance of demonstrating improvement in 12MWT with galsulfase. These selection criteria potentially limit the generalizability of findings to milder or more severe disease.

The study duration of 24 weeks was selected for ASB-03-05 to enable the detection of changes in surrogates of endurance (12MWT, 3MSCT) based on findings from an earlier phase study in the clinical development program and also on the design of other phase 3 trials of ERT. However, the study duration was insufficient to capture end points reflecting the complications and impairments associated with MPS VI — i.e., the need for orthopaedic surgery or mobility aids, or changes in height or linear growth. Data on the effects of galsulfase on mortality would also be of value, although it is acknowledged that it would impractical, in the context of an RCT, to capture the years or decades of follow-up required to assess this outcome meaningfully.

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. The key efficacy findings are presented in Table 6.

3.6.1 Survival

Survival was not studied as an efficacy outcome in study ASB-03-05.[15] No deaths were reported during the 24-week RCT period.

3.6.2 Disease progression

Disease progression, as defined in the CDR systematic review protocol based on clinical expert input, included: a) initiation of wheelchair or walking aid use; b) requirement for corrective orthopaedic surgery; c) cardiac failure; d) respiratory failure (e.g., requirement for tracheotomy) (Table 2). This definition was intended to reflect the most objective and important clinical sequelae of MPS VI, rather than all measures of disease progression reported in the literature or used in clinical practice.

Wheelchair or walking aid use and corrective orthopaedic surgery were reported as planned end points as part of the assessment of health resource utilization; however, no results were reported for either the RCT phase[15] or extension phase.[16] Cardiac failure and respiratory failure were not studied as efficacy outcomes in study ASB-03-05.[15] One patient in the placebo group experienced cardiac failure reported as an SAE (Table 7). Two patients (one in the galsulfase group, one in the placebo group) experienced tracheotomy events reported as SAEs during the 24-week study period (Table 7).

3.6.3 Endurance

a) Twelve-minute walk test

The 12MWT was the primary outcome in study ASB-03-05. The primary analysis of the 12MWT employed a longitudinal repeated measures model. As shown in Table 9 to Table 11 and Figure 2, the 12MWT distance for patients in the placebo group remained relatively unchanged from baseline to 24 weeks of follow-up (mean change ± SD: 26 ± 122 m). On the other hand, patients in the galsulfase group showed a steady improvement with a levelling off after week 18. The galsulfase group demonstrated a total mean increase in distance walked in the 12MWT of 109± 154 m from baseline to week 24 (Table 11). At week 24, the adjusted difference (mean ± SE) between the galsulfase and placebo groups was 92 m (95% CI, 11 to 172) in favour of galsulfase (*P* = 0.025).

Subgroup and sensitivity analyses

[redacted] respectively. These estimates support the findings from the primary analysis (i.e., all randomized patients) (Table 12).

Other sensitivity analyses were performed to evaluate the robustness of the 12MWT data. These included analyses of baseline and week 24 data only, rather than longitudinal analysis (Table 11); 6MWT (Table 18 and Table 19); the influence of study centre and baseline characteristics (such as age, gender, etc.); and other longitudinal analyses models (Table 13 to Table 16). Overall, the results of all sensitivity analyses were similar to the primary analysis.

No data were reported for the clinically important subpopulations specified in the protocol for this review (Table 2), such as patients younger than one year, adults, and patients with cardiac failure or tracheostomy.

Responder analysis based on 12-minute walk test

[redacted] (Table 17).

Three-minute stair climb test

The 3MSCT was the secondary outcome in study ASB-03-05. The placebo group remained relatively unchanged over time (mean ± SD: 31 ± 18 stairs per minute at baseline and 33 ± 20 at week 24). For the galsulfase group, baseline 3MSCT was 19 ±13 stairs per minute, and this increased to 27 ± 17 stairs per minute at week 24 (Table 20). Compared with placebo, the adjusted climb rate from the longitudinal model for patients in the galsulfase group increased by an average of 5.7 ± 2.9 stairs per minute (*P* = 0.053) at week 24. The adjusted means over time are provided in Table 22 and Table 23**Error! Reference source not found.**

Similar improvement in the 3MSCT was observed in the subgroup analysis of walk-eligible patients, and patients with ≤ 400 m on the 12MWT (Table 23).

3.6.4 Height and weight

[redacted]

3.6.5 Quality of life

QoL was not studied as an efficacy outcome in study ASB-03-05.

3.6.6 Pulmonary function

There were no statistically significant differences between the galsulfase and placebo groups in forced viral capacity (FVC) or forced expiratory volume in one second (FEV_1) (Table 24).

3.6.7 Skeletal and soft tissue function

Shoulder ROM, joint pain, and coin pick-up were assessed as tertiary outcomes. At baseline, the parameters were well balanced between treatment groups (Table 25). The mean differences between groups in change from baseline at week 24 were small and not statistically significant for any of these outcomes (Table 26).

3.6.8 Health resource utilization

Health resource utilization — including antibiotic use, hospitalizations, days missed from school and work, requirement for wheelchair or other ambulatory aid, and requirement for positive airway pressure during sleep — were assessed at baseline. [redacted].[15] It was also reported that there were average reductions of 0.237 surgical or diagnostic procedures and 0.53 hospitalizations per patient in the galsulfase group compared with placebo at week 24 (statistical significance not reported).[19] No other health resource utilization data were reported.

3.6.9 Sleep function test

Sleep function was not studied as an efficacy outcome in study ASB-03-05.

3.6.10 Hearing function

Hearing function was not studied as an efficacy outcome in study ASB-03-05.

3.6.11 Ophthalmology evaluation

Ophthalmologic assessments were performed at baseline. According to the study protocol, visual acuity and corneal photography were scheduled to be assessed at week 24. However, these outcomes were not reported in either the RCT[14] or the extension phase.[16]

3.6.12 Size of liver and spleen

Liver and spleen size was not studied as an efficacy outcome in study ASB-03-05. No patients were reported to have hepatomegaly or hepatosplenomegaly as an AE in the galsulfase group. In the placebo group, three (15%) patients and two (10%) with hepatomegaly and splenomegaly were reported, respectively (Appendix 4, Table 31).

3.6.13 Urinary glycosaminoglycan

Urinary GAG levels were similar in the galsulfase and placebo groups at baseline. Urinary GAG levels in the placebo group were (mean ± SD) 330 ± 114 mcg/mg creatinine at baseline and 317 ± 8 mcg/mg creatinine at week 24 (Table 27). In the galsulfase group, the baseline urinary GAG level (mean ± SD) was 346 ± 128 mcg/mg creatinine; at week 24, it was 85 ± 35 mcg/mg creatinine, representing a mean per cent reduction of 73% (Table 27). The mean level decreased rapidly after initiation of treatment until week 6 and continued to slowly decrease thereafter (see Figure 3). Adjusted for baseline urinary GAG levels, the estimated difference between placebo and galsulfase (mean ± SE) at week 24 was –227 ± 18 mcg/mg creatinine (95% CI, –265 to –190, $P < 0.001$) (Table 28). In terms of responders on urinary GAG (defined as ≥ 50% reduction from baseline to week 24), 17 of the 19 patients (89.5%) in the galsulfase group were considered responders, while no patients in the placebo group satisfied this criterion (Table 29).

TABLE 6: KEY EFFICACY OUTCOMES

	ASB-03-05	
OUTCOMES	Galsulfase (N = 19)	Placebo (N = 20)
12MWT (m, mean ± SD)		
N	19	20
Baseline	227 ± 170	381 ± 202
Week 24	336 ± 227	399 ± 217
Change from baseline at week 24	109 ± 154	26 ± 122
Adjusted mean difference at week 24, mean (95% CI)[a]	92 (11 to 172)	
P value	0.025	
Number of responders for 12MWT[b]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
3MSCT (stairs/min, mean ± SD)		
N	19	20
Baseline	19.4 ± 12.9	31.0 ± 18.1
Week 24	26.9 ± 16.8	32.6 ± 19.6[c]
Change from baseline at week 24	7.4 ± 9.9	2.7 ± 6.9[c]
Adjusted mean difference at week 24, mean (95% CI)	5.7 (–0.1 to 11.5)	
P value[a]	0.053	

3MSCT = three-minute stair climb test; 12MWT = 12-minute walk test; ASB = arylsulfatase B (or *N*-acetylgalactosamine-4-sulfatase); CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; GAG = glycosaminoglycan; MD = mean difference; min = minute SD = standard deviation.

[a] Mean at week 24: adjusted for baseline.

[b] A "responder" for 12MWT was defined as a patient who improved more than 80 m from baseline to week 24.

[c] 19 patients included in this analysis.

Source: Clinical Study Report p. 94, 198, 246.

3.7 Harms

Only those harms identified in the review protocol are reported below (see Section 2.2, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data. The main harm outcomes are presented in Table 7.

3.7.1 Adverse events

All patients in both treatment groups experienced at least one AE during the study (Table 30 to Table 31). [redacted].

3.7.2 Serious adverse events

Seven patients (three in the galsulfase group and four in the placebo group) experienced a total of 15 SAEs during the 24 weeks of the study (Table 7). Numerically more SAEs occurred in patients in the placebo group (12 SAEs) than in the galsulfase group (three SAEs). [redacted] (Table 7).

3.7.3 Withdrawals due to adverse events

No patients discontinued the study or drugs due to AEs.

3.7.4 Notable harms

[redacted] Neither was performed during the infusion period. The patient in the placebo group underwent the tracheotomy due to severe airway obstruction, while the patient treated with galsulfase underwent the tracheotomy due to apnea, which was judged by the investigator as possibly related to galsulfase (Table 7).

Infusion-associated reactions: AEs occurring during infusion that were judged to be possibly, probably, or definitely related to study drug were considered infusion-associated reactions (IARs). Ten patients in the galsulfase group and four patients in the placebo group experienced an IAR. IARs were considered anaphylactoid reactions if they recurred during multiple infusions, improved with a decrease in study drug infusion rate or interruption of infusion, and/or improved with additional antihistamine, antipyretic, or steroid treatment. Eleven patients in the galsulfase group and eight in the placebo group experienced infusion-associated events (IAEs) (Table 7).

[redacted]).[15]

TABLE 7: HARMS

	ASB-03-08	
AEs	**Galsulfase**	**Placebo**
Patients with at least 1 AE, n (%)	19 (100)	20 (100)
Most common AEs		
Abdominal pain	9 (47)	7 (35)
Headache	8 (42)	12 (60)
Pyrexia	8 (42)	8 (40)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SAEs		
Patients with at least 1 SAE, n (%)	3 (16)	4 (20)
[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]

AE = adverse event; ASB = arylsulfatase B (or *N*-acetylgalactosamine-4-sulfatase); IAR = Infusion associated reaction; OD = optical density; SAE = serious adverse event; WDAE = withdrawal due to adverse events.
[a] AEs occurring in 2% more in galsulfase group than that in placebo group.
Source: Clinical Study Report.[15]

4. DISCUSSION

4.1 Summary of available evidence

The evidence for this review was derived from one phase 3, DB, randomized, placebo-controlled study (ASB-03-05) comprising 39 patients aged seven years and older (three patients between the ages of five years and seven years of age were permitted, all of whom were randomized to the placebo group) with a confirmed diagnosis of MPS VI. Patients were randomly assigned to either weekly galsulfase 1 mg/kg or matching placebo solution for 24 weeks. While the population studied was likely reflective of patients with MPS VI treated in Canada, according to the clinical expert consulted by CDR, only six adults were enrolled in the trial. As well, the lack of data for children younger than seven years of age is a limitation, as such patients will likely be considered for treatment in clinical practice. Imbalances between groups were noted in some key baseline characteristics, particularly 12MWT distance and 3MSCT, both of which were considerably higher at baseline in the placebo group. The ASB-03-05 trial was primarily designed to assess the effect of galsulfase on surrogate markers of endurance and mobility — i.e., 12MWT and 3MSCT — and little or no data were reported for other outcomes of direct relevance to patients, such as disease progression, growth, QoL, functional status, or survival. Furthermore, the lack of validation of the 12MWT and 3MSCT in MPS VI made it difficult to assess the clinical relevance of the observed improvements with galsulfase on these outcomes. Other key limitations of the ASB-03-05 study included the lack of data on analgesic use during the study, which precluded assessment as to whether imbalances in their use may have biased the 12MWT and 3MSCT results, and lack of adjustment for multiple statistical testing performed on the secondary outcomes and tertiary outcomes.

4.2 Interpretation of results

4.2.1 Efficacy

The primary efficacy outcome in ASB-03-05 was 12MWT, a marker of endurance, at 24 weeks. By comparison, the review protocol and input from patient groups considered survival and disease progression to be key efficacy outcomes followed by markers of endurance and height and weight percentiles. Survival and disease progression were not reported in ASB-03-05, nor was this study long enough to meaningfully capture these outcomes. A statistically significant increase in 12MWT was observed from baseline to week 24 favouring galsulfase (adjusted mean difference at 24 weeks: 92 m; 95% CI, 11 to 172). Results from various pre-specified subgroup and sensitivity analyses were directionally consistent with the primary analysis. While the findings for 12MWT were statistically significant and appeared robust, the clinical significance of the observed change is uncertain in the absence of validation studies and a MCID for this outcome in patients with MPS VI. Hence, the extent to which the improvement in 12MWT will translate to stabilization or improvement in outcomes of direct relevance to patients — namely pain, fatigue, ability to perform activities of daily living, QoL, and need for mobility aids — is uncertain. Despite these limitations, the FDA agreed to the use of 12MWT as an acceptable primary efficacy outcome for MPS VI in the design phase of ASB-03-05, as it was considered an adequate measure of the functional limitations of the disease. Another concern about the 12MWT findings was the potential ceiling effect in the placebo group, since the baseline mean 12MWT distance was 381 m, close to the threshold for inclusion (< 400 m). It is not unreasonable to suspect that the extent of improvement possible for patients in the placebo group may have been less than in the galsulfase group. However, in the 72-week extension phase of the trial, patients in the placebo group switched to galsulfase treatment demonstrated a mean increase in 12MWT distance of 118 m ($P < 0.01$), a finding that somewhat mitigates the concern regarding a ceiling effect.

Based on the opinion of the clinical expert consulted for this review, individual 12MWT results could have provided greater insights into the range of improvement conferred by galsulfase than simply the mean difference between treatment groups; however, such data were not reported.

[redacted]but the responder analysis may have lacked sufficient statistical power to detect a difference between groups. While arbitrary, the clinical expert consulted by CDR considered that the threshold used in the trial for defining response (≥ 80 m) likely represented a significant improvement.

Findings from the 3MSCT were supportive of the results for 12MWT, in that they showed that patients in the galsulfase group climbed an average of approximately six additional stairs per minute than patients in the placebo group at week 24. However, the difference was not statistically significant (*P* = 0.053).

MPS VI is characterized by impairment in the enzymatic degradation of dermatan sulfate, resulting in accumulation and clinical manifestations of the disease. The presence of elevated urinary dermatan sulfate is used to aid in the diagnosis of MPS VI, and total urinary GAG levels are also used for monitoring disease activity. In study ASB-03-05, it was reported that the urinary GAG level was statistically significantly lower than in the placebo group at week 24 (mean ± SE: –227 ± 18 mcg/mg creatinine; 95% CI, –265 to –190, *P* < 0.001). In terms of responders on urinary GAG (defined as ≥ 50% reduction from baseline to week 24), 89.5% of patients in the galsulfase group were considered responders compared with no patients in the placebo group. While urinary GAG level is a biologically relevant surrogate outcome, it is poorly correlated with disease activity or clinical end points according to the clinical expert consulted by CDR. Therefore, the clinical significance of the observed reduction in urinary GAG levels with galsulfase is uncertain.

Height, pulmonary function, and skeletal and soft tissue function (e.g., ROM of shoulder, joint pain and stiffness, coin pick-up test) were briefly reported. No differences were observed between the two treatment groups on these outcomes. Due to the short duration of ASB-03-05, there was likely insufficient time to detect improvements in height. Therefore, the effect of galsulfase on this outcome is inconclusive until longer-term data are available.

[redacted]

[redacted]
(APPENDIX 6).

Based on the selection criteria and baseline characteristics of study ASB-03-05, the clinical expert consulted for this review pointed out that the patients included had MPS VI that was clinically moderate in severity. Therefore, the extent to which the results can be generalized to patients with milder or more severe disease is uncertain. The age of patients ranged between five and 29 years. The majority (85%) of patients were under 18 years of age. Thus, the findings would appear most generalizable to the

adolescent and pre-adolescent populations. The clinical expert indicated that an earlier initiation of ERT may theoretically be more beneficial in preventing the sequelae of MPS VI compared with delayed initiation, although there is as yet no direct evidence of this. Hence, the lack of data for the use of galsulfase in children younger than seven years of age, and in patients with milder disease, represents an important limitation, one that may pose challenges in using galsulfase in such patients, because it could be difficult to monitor response to therapy. It is noteworthy that experience with galsulfase in younger children has been reported in observational studies. For example, a retrospective study of the medical records of 34 patients younger than five years of age suggested that galsulfase ERT was effective in slowing progression and improving certain aspects of MPS VI disease, although the authors suggested that a long-term study was needed to evaluate the benefits and safety of early treatment.[20]

Patients' expectations for galsulfase are to stabilize the disease progression of MPS VI, improve QoL, and reduce the need for hospital visits, medical interventions, and physician appointments. However, these outcomes were not assessed in ASB-03-05. Furthermore, the correlation between the outcomes that were assessed, i.e., 12MWT, stair climb test, and patient-important outcomes is uncertain. Some of the evidence gaps regarding patient-important outcomes may be filled by data from long-term observational studies rather than an RCT. One such study has been published: a 10-year follow-up study of 121 patients with MPS VI initially surveyed in 2001–2002, many of whom were eventually treated with galsulfase for several years (mean ± SD: 6.8 ± 2.2 years).[5] It confirmed the findings of ASB-03-05 with respect to endurance as measured by walking distance, and suggested substantially improved longevity with galsulfase therapy (hazard ratio for mortality of 0.11). Long-term galsulfase therapy was also reportedly associated with improvements in pulmonary function and stabilization of cardiac function. However, the cross-sectional nature of the study, the relatively small control group of untreated patients (representing only 7% to 12% of the sample, depending upon the outcome), and the substantial differences in age and other baseline characteristics between treated and untreated patients, make it difficult to conclude that the apparent differences in outcome are entirely attributable to galsulfase therapy.

4.2.2 Harms

Overall, AEs in ASB-03-05 were common in both treatment groups. All patients experienced at least one AE during the 24-week study period. [redacted] All patients except one, in the placebo arm, completed the study. Eleven patients in the galsulfase group and eight in the placebo group experienced IAEs. There were no WDAEs and no deaths reported during the study.

All 19 patients assigned to the galsulfase group developed immunoglobulin G (IgG) antibody levels (≥ 0.20 optical density [OD] per mcL serum) during the 24-week study. The clinical expert consulted for

this review indicated that antibodies against galsulfase may not be neutralizing antibody. Therefore, the therapeutic efficacy of galsulfase may not be affected by the presence of antibodies.

The extension phase of study ASB-03-05 was designed for [redacted]; safety data were available for [redacted] of open-label galsulfase treatment ([redacted]). [redacted] (APPENDIX 6).

4.3 Potential place in therapy

The information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

ERT with galsulfase can be indicated in patients with low enzyme activity and is aimed at reducing the amount of storage product, mostly dermatan sulfate, to modify the disease course. Galsulfase is not a cure and does not treat all aspects of MPS VI. The most consistent documented response is an increase in walking speed, determined as the distance travelled in either six or 12 minutes. Other than the distance walked, the studies do not document how this change improved QoL, whether it reduced wheelchair use, and/or decreased the need for walking aids, hospitalizations, the use of oxygen, surgical care, or clinical interventions. Other measures, such as the 3MSCT, show inconsistent responses between different studies. Nevertheless, based on clinical experience and the response demonstrated in other studies, the observed increase in walk test distances likely results in a meaningful improvement in the daily lives of patients with MPS VI, with improved mobility and reduced pain when they are trying to walk. This suggests that patients likely to benefit from ERT with galsulfase are those who are mobile but have ambulatory difficulty. There may, however, be an indication to use ERT in children who are diagnosed with MPS VI before they start walking. Early treatment has been shown to be more favourable in a sibling study.[21] The benefit of ERT in patients who are not ambulatory is unproven, and given the lack of consistent and clinically relevant improvement in pulmonary function (FVC), there may be little or no benefit to starting or continuing ERT in a patient who is not ambulatory. Nevertheless, a trial of ERT may be considered in patients with MPS VI who are non-ambulatory if there are pre-defined outcomes — e.g., cardiac, ROM, pulmonary (FVC, FEV_1), QoL, or hearing — that would be expected to improve the QoL or functional status of the patient. However, compared with 12MWT, evidence for the benefit of galsulfase on these other outcomes is poor. Unfortunately, published guidelines do not provide a systematic review of whether the responses to ERT in MPS VI are consistent and give the impression of a wider indication for use than suggested by the actual data.[22]

Patients who are considered responsive to galsulfase see an initial reduction in urinary GAG excretion that can be seen by six weeks after start of ERT. Unresponsiveness may manifest by the development of neutralizing anti-galsulfase IgG antibodies (although not all such antibodies are neutralizing) after 24 weeks of therapy, and some patients see an increase in urinary GAG. These patients may not be receiving benefits from ERT. The development of antibody titres is also higher in infants treated with the disease.

HSCT is another option for treating MPS VI. While a historical review of more than 40 cases where HSCT was used showed a three-year survival of 66%,[10] new management options such as the use of a non-carrier sibling or haploidentical donors, improved conditioning regimens, or the use of allogeneic peripheral-mobilized CD34+ stem cells have resulted in improved outcomes with HSCT for mucopolysaccharide storage diseases.[23] In patients who respond to HSCT, the effect can be sustained, making weekly infusions of ERT unnecessary. There may be a role for ERT in the adjuvant treatment of

patients who are preparing to undergo HSCT and in the first few months after HSCT, similar to practices used in MPS I. HSCT may be a consideration in more severe disease and early on in the disease course, such as in infants, or in those with a known severe genotype[24] that may produce high antibody titres, or when non-responsiveness to ERT is manifest. It would be irresponsible for a practitioner to consider ERT as the only treatment option in discussion with families, since all the options with their inherent risks and benefits should be reviewed.

Any application for ERT should disclose whether all treatment options were discussed, that the appropriate clinical indications are targeted (improved mobility in patients who are ambulatory), that appropriate expectations are placed in terms of the type of response expected, that appropriate monitoring is set up to measure the response, and that stop criteria are established for stopping ERT. ERT should only be given by a physician experienced in the management of mucopolysaccharide storage diseases. Stop criteria should be set by a committee of physicians, nurses, allied health professionals, etc. There are currently no Canadian guidelines to advise on stop criteria, and they can be challenging to enforce in practice. From the data on galsulfase, the only evidence for an area of improvement is the 12MWT. Therefore, when a patient is no longer ambulatory, it does not appear that any of the other purported benefits of the drug (such as respiratory) would be obtained. Milder benefits on joint motion may continue, but this has not been clearly demonstrated by the data. Goals of care should be reviewed annually with the family by the treatment team. From a reimbursement perspective, it could be specified that approvals are for one year, after which time a re-evaluation is necessary. This has been implemented in at least one jurisdiction for ERT for patients with MPS IV (Morquio A syndrome). Re-evaluation could occur through a board of physicians that reviews requests for the annual renewal of ERT based on an update of clinical status from the providing physician.

In terms of the practical aspects of galsulfase administration, it appears that AEs are less common after 24 weeks, which makes it possible to consider home infusion in some patients. Prior to 24 weeks, infusion in hospital or a medical clinic with access to emergency airway management may be necessary.

5. CONCLUSIONS

In a single RCT (ASB-03-05) of 39 patients, galsulfase IV infusion once weekly was shown to improve 12MWT distance compared with placebo in patients seven years of age and older with a confirmed diagnosis of MPS VI, most of whom were adolescents and pre-adolescents. There were no data reported for outcomes of direct relevance to patients, such as disease progression, QoL, or survival. Although 12MWT is accepted by regulatory authorities as an outcome in MPS VI, the clinical importance of the observed improvement is unclear in the absence of studies validating this outcome in patients with MPS VI. Therefore, it is unclear whether the findings for 12MWT will translate to improved survival, disease stabilization, reduced need for surgical intervention, or improved QoL. Results were either not statistically significant or statistical comparisons were not made for other outcomes of interest to this review, including the 3MSCT, height, and shoulder ROM. Galsulfase treatment was more commonly associated with pyrexia, abdominal pain, [redacted] dyspnea, chills, and rash versus placebo. Numerically, more SAEs occurred in the placebo group than in the galsulfase group. There were no WDAES or deaths reported during the study. No additional safety signals were identified in the open-label extension trial at three years after ASB-03-05 baseline.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief description of patient group(s) supplying input

Patient input was provided by two groups: the Isaac Foundation for Mucopolysaccharidosis (MPS) Treatment and Research, and the Canadian Society for Mucopolysaccharide and Related Diseases (the Canadian MPS Society). The Isaac Foundation's mission is to fund innovative research projects that aim to find a cure for MPS. Additionally, it provides support for families of individuals suffering from MPS and advocate on their behalf for government funding of treatments. The Canadian MPS Society provides support to individuals and families affected with MPS and related diseases, educates medical professionals and the general public about MPS, and raises funds for research for a cure for MPS and related diseases.

The Isaac Foundation receives funding from BioMarin, Shire, and Janssen Pharmaceuticals. The Canadian MPS Society receives funding from Genzyme and BioMarin Pharmaceuticals. Both groups declared no conflict of interest in the preparation of the patient input submission.

2. Condition-related information

Information for this section originated from patient conversations (including with parents of patients), an online survey of Canadian and international mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) patients receiving therapy and their caregivers, as well as data from the literature.

MPS VI is a disease that has numerous life-altering, life-threatening, and very progressive symptoms. The impact of MPS VI on the musculoskeletal system was consistently described as producing significant pain, and loss of function and quality of life (QoL). One parent described the limitations that MPS VI imposed on their son's activities of daily living: "his hands are incredibly impacted, which leads to difficulty gripping objects, opening jars, dressing himself, and tying his shoes. His shoulders became very stiff and range of motion in his shoulders decreased rapidly […] and this has prevented him from being able to raise them over his head very effectively. This impacts his ability to wash his hair and dress himself." Caregivers also described that the progressive loss of function from the disease resulted in loss of QoL from losing the ability to perform enjoyable activities, including riding a bike, playing team sports, playing musical instruments, and writing or drawing.

The impact on caregivers as a result of extensive care requirements, long hospital lengths of stay, multiple surgical interventions, and frequent medical appointments of patients with MPS VI included frequent missed work, particularly for those living far from specialized centres.

3. Current therapy-related information

Information for this section originated from patient conversations, as well as data from the literature.

Prior to galsulfase, MPS was treated by managing symptoms as they appeared. Essentially, a long-term palliative approach to managing the disease was taken. This is still true for patients who do not gain access to treatment with galsulfase.

All interviewed patients and caregivers reported stabilization of their condition and improvement in their QoL following initiation of galsulfase. One parent noted about her child with MPS VI: "Her energy

increased dramatically. Her stamina and endurance increased dramatically. Her strength is improved; her mood is better (due to better sleeping and being able to do more physical activities). Her Maroteaux-Lamy symptoms have been slowed down dramatically. All medical appointments this past 12 months have been encouraging. She has shown improvements in all aspects of her health, including growth." One parent described stabilization of her son's disease with galsulfase, but added that "the symptoms that appeared prior to starting treatment are debilitating," noting persistent disability from irreversible musculoskeletal deformities.

Limitations of galsulfase focused on access to the drug and infusion facilities. Interviewed patients and caregivers denied experiencing any serious or life-threatening infusion reactions as a result of galsulfase, and reported that mild infusion-related reactions were tolerable and did not result in discontinuation of galsulfase. The primary concern expressed by caregivers was travel time related to the weekly four-hour galsulfase intravenous (IV) injections, which in some cases required two days per week.

No further information was provided regarding other treatments, such as supportive care, for MPS VI.

4. Expectations about the drug being reviewed

Information for this section originated from patient conversations (including with parents of patients), an online survey of Canadian and international MPS VI patients receiving therapy and their caregivers, as well as data from the literature.

The expectations for galsulfase are that it will lead to stabilization of MPS VI regardless of when treatment is initiated. Further, patient groups expect that this stabilization will result in an increase in QoL, as well as fewer hospital visits, medical interventions, and physician appointments. For caretakers and/or patients, this is expected to result in less time off work or school, and less stress for family members. One parent noted: "Our daughter is a prime example of the benefit of enzyme replacement therapy with galsulfase; without it she would have numerous health issues as a result of non-treatment, her quality of life would be greatly diminished, and her life expectancy shortened substantially."

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, 2015
Alerts:	Bi-weekly search updates until January 20, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used 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
.kw	Keyword
.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		
Line #	**Search Strategy**	**Results**
1	N-acetylgalactosamine-4-sulfatase/ use pmez	184
2	(galsulfase* or Naglazyme* or Naglazyzme* or Aryplase* or BM 102 or BM102 or UNII-59UA429E5G or 552858-79-4 or arylsulfatase B or rhASB or N-acetylgalactosamine-4-sulfatase or ARSB).ti,ot,ab,sh,hw,rn,nm,kw. use pmez	583
3	1 or 2	583
4	*N-acetylgalactosamine-4-sulfatase/ use oemezd	338
5	*galsulfase/ use oemezd	67
6	(galsulfase* or Naglazyme* or Naglazyzme* or Aryplase* or BM 102 or BM102 or UNII-59UA429E5G or arylsulfatase B or rhASB or N-acetylgalactosamine-4-sulfatase or ARSB).ti,ab. use oemezd	712
7	4 or 5 or 6	918
8	conference abstract.pt.	1976427
9	7 not 8	769
10	3 or 9	1352
11	remove duplicates from 10	859

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 2015
Keywords:	Naglazyme, galsulfase, Mucopolysaccharidosis, Maroteaux-Lamy syndrome
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/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Harmatz P et al. (2014)[3]	Comparator not of interest
Harmatz P et al. (2004)[25]	Study design not of interest
Harmatz P et al. (2005)[26]	Study design not of interest
Harmatz P et al. (2010)[27]	Study design not of interest
Harmatz P et al. (2008)[28]	Study design not of interest
Harmatz P et al. (2005)[29]	Study design not of interest

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 8: STUDY DRUG INFUSIONS

	Galsulfase (N = 19)	Placebo (N = 20)
Infusions per patient		
Mean (SD)	[redacted]	[redacted]
Range	[redacted]	[redacted]
Percentiles (25th, median, 75th)	[redacted]	[redacted]

SD = standard deviation.
[a] One patient discontinued from the study after week 4 infusion.
Source: Clinical Study Report, p. 295.

TABLE 9: TWELVE-MINUTE WALK TEST SUMMARY OF OBSERVED DATA

	Observed (Raw) Data							
	Galsulfase			Placebo			Difference (Galsulfase — Placebo)	
	n	Mean	SD	n	Mean	SD	Mean	SE
Baseline	19	227	170	20	381	202	–154	60
Week 6	19	290	201	19	383	213	–93	67
Week 12	19	303	216	19	398	208	–94	69
Week 18	18	344	202	19	399	226	–55	70
Week 24	19	336	227	19	399	217	–63	72

SD = standard deviation; SE = standard error.
Source: Clinical Study Report, p. 78.

TABLE 10: TWELVE-MINUTE WALK TEST SUMMARY (ADJUSTED DATA)

	Adjusted Data[a]					
	Galsulfase		Placebo		Difference (Galsulfase — Placebo)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Baseline	306	—	306	—	0	—
Week 6	378	322, 434	316	263, 369	62	–18 to 142
Week 12	392	336, 447	331	278, 384	61	–20 to 141
Week 18	421	365, 478	332	279, 385	89	9 to 170
Week 24	424	368, 480	332	280, 385	**92**	**11 to 172**

12MWT = 12-minute walk test; CI = confidence interval.
[a] Adjusted for baseline 12MWT.
Source: Clinical Study Report, p. 78.

TABLE 11: TWELVE-MINUTE WALK TEST: SUMMARY OF MEASURES FOR BASELINE, WEEK 24, AND THEIR DIFFERENCES (METRES)

	Galsulfase			Placebo			Mean Difference	*P* value
	Baseline	Week 24	Change	Baseline	Week 24	Change		
Observed (raw)								
N	19	19	19	20	19	19	—	—
Mean ± SD	227 ± 170	336 ± 227	109 ± 154	381 ± 202	399 ± 217	26 ± 122	[redacted]	—
Range	9 to 623	5 to 797	–48 to 440	46 to 685	64 to 747	–266 to 267	—	—
Adjusted data[b]								
Mean ± SE	—	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12MWT = 12-minute walk test; SD = standard deviation; SE = standard error.
[a] Mean ± SE, mean difference of changes from baseline.
[b] For adjusted means: week 24 estimate was adjusted for baseline 12MWT.
Source: Clinical Study Report, p. 79.

TABLE 12: TWELVE-MINUTE WALK TESTS FOR WALK-ELIGIBLE AND ≤ 400 M SUBSETS AT WEEK 24

	N		Baseline (Mean ± SD)		Adjusted Difference[a] (Mean ± SE) (Galsulfase — Placebo)	*P* value
Analysis Set	Galsulfase	Placebo	Galsulfase	Placebo		
All patients Randomized	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walk-eligible subset	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 400 m subset	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

SD = standard deviation; SE = standard error.

TABLE 13: TWELVE-MINUTE WALK TEST — USING ONLY BASELINE AND WEEK 24 DATA (I.E., NOT MULTIPLE REPEATED MEASURES)

Method	Mean ± SE (Galsulfase – Placebo)	95% CI	*P* value
ANOVA[a]	[redacted]	[redacted]	[redacted]
T-test on the difference of changes from baseline	[redacted]	[redacted]	[redacted]
Wilcoxon test on the difference of change from baseline	[redacted]	[redacted]	[redacted]

[redacted]

ANOVA = analysis of variance; CI = confidence interval; SE = standard error.

TABLE 14: TWELVE-MINUTE WALK TEST — WALK-ELIGIBLE SUBSET: USING ONLY BASELINE AND WEEK 24 DATA

Method	Mean ± SE (Galsulfase — Placebo)	95% CI	*P* value
ANOVA[a]	[redacted]	[redacted]	[redacted]
T-test on the difference of changes from baseline	[redacted]	[redacted]	[redacted]
Wilcoxon test on the difference of changes from baseline	[redacted]	[redacted]	[redacted]

[redacted]

ANOVA = analysis of variance; CI = confidence interval; SE = standard error.

TABLE 15: TWELVE-MINUTE WALK TEST — ≤ 400 M SUBSET: USING ONLY BASELINE AND WEEK 24 DATA

Method	Mean ± SE (Galsulfase – Placebo)	95% CI	*P* value
ANOVA[a]	[redacted]	[redacted]	[redacted]
T-test on the difference from baseline	[redacted]	[redacted]	[redacted]
Wilcoxon test on the difference from baseline	[redacted]	[redacted]	[redacted]

[redacted]

ANOVA = analysis of variance; CI = confidence interval; SE = standard error.

TABLE 16: TWELVE-MINUTE WALK TEST — MODELS INCLUDING BASELINE COVARIATES

Model Including	Mean (m) (Galsulfase — Placebo)	95% CI	*P* value
Age	[redacted]	[redacted]	[redacted]
Age, gender	[redacted]	[redacted]	[redacted]
Age, gender, height	[redacted]	[redacted]	[redacted]
Age, height	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]
Gender, height	[redacted]	[redacted]	[redacted]
Height	[redacted]	[redacted]	[redacted]

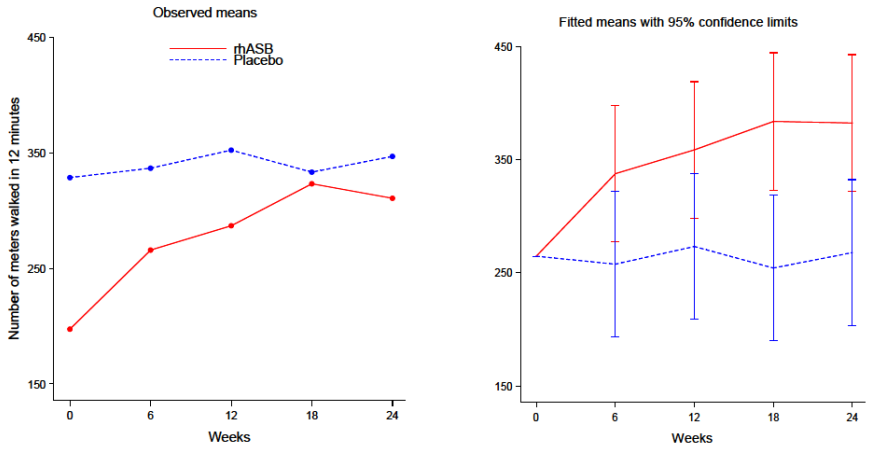
[redacted]

CI = confidence interval.

[redacted]

Source: Clinical Study Report, p. 76.

FIGURE 2: OBSERVED (A) AND ADJUSTED (B) MEANS OF TWELVE-MINUTE WALK TEST OVER TIME: WALK-ELIGIBLE SUBSET



Raw data Adjusted for baseline 12MWT

12MWT = 12-minute walk test; rhASB = recombinant human *N*-acetylgalactosamine-4-sulfatase (galsulfase).

Source: Clinical Study Report, p. 80.

TABLE 17: NUMBER OF RESPONDERS IN THE 12-MINUTE WALK TEST

Responders,[a] n/N (%)	Observed Data	
	Galsulfase	Placebo
	N = 19	N = 20
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
All sites	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

TABLE 18: FIRST 6 MINUTES OF THE 12-MINUTE WALK TEST: SUMMARY OF MEANS OVER TIME (METRES)

	Observed (Raw) Data					Adjusted (Predicted) Data[a]		
	Galsulfase		Placebo		Difference (Galsulfase — Placebo)	Galsulfase	Placebo	Difference (Galsulfase — Placebo)
	n	Mean (SD)	n	Mean (SD)	Mean (SE)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

CI = confidence interval; SE = standard error; SD = standard deviation.

TABLE 19: FIRST 6 MINUTES OF THE 12-MINUTE WALK TEST: SUMMARY OF MEASURES FOR BASELINE AND WEEK 24 (METRES)

	Galsulfase			Placebo			Difference
	Baseline	Week 24	Change	Baseline	Week 24	Change	
Observed (raw)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted							
Mean ± SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

SE = standard error; SD = standard deviation.

TABLE 20: THREE-MINUTE STAIR CLIMB RATE: SUMMARY OF MEANS OVER TIME (STAIRS PER MINUTE)

	Observed (Raw) Data							
	Galsulfase			Placebo			Difference	
	n	Mean	SD	n	Mean	SD	Mean	SE
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

SE = standard error; SD = standard deviation.

TABLE 21: THREE-MINUTE STAIR CLIMB RATE: SUMMARY OF MEANS OVER TIME

	Adjusted for Baseline 3MSCT					
	Galsulfase		Placebo		Difference (Galsulfase — Placebo)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3MSCT = three-minute stair climb test; CI = confidence interval.

TABLE 22: THREE-MINUTE STAIR CLIMB RATE: BASELINE, WEEK 24, AND THEIR DIFFERENCES (STAIRS PER MINUTE)

	Galsulfase			Placebo			Difference in Changes (Mean ± SE)
	Baseline	Week 24	Change	Baseline	Week 24	Change	
Observed (raw)							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted[b]							
Mean ± SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

SE = standard error; SD = standard deviation.

TABLE 23: SUMMARY OF THREE-MINUTE STAIR CLIMBS

Population	Per Cent of In-Window Stair Climbs Reaching the Top	Difference (Adjusted)[a] (Galsulfase — Placebo)			
		Stairs/Minute		Number of Stairs Climbed	
		Mean ± SE	*P* value	Mean ± SE	*P* value
All randomized	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walk-eligible subset	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 400 m subset	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

SE = standard error.

TABLE 24: SUMMARY OF CHANGES IN PULMONARY FUNCTION TESTS

Test (Unit)	N[a]		Estimated Difference (Mean ± SD)	95% CI	*P* value
	Galsulfase	Placebo			
FVC (L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 (L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

CI = confidence interval; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; SD = standard deviation.

TABLE 25: JOINT PAIN, RANGE OF MOTION, AND COIN PICK-UP — BASELINE VALUES

	Galsulfase		Placebo	
End Point	N	Mean ± SD	N	Mean ± SD
Joint pain,[a] pre-activity	[redacted]	[redacted]	[redacted]	[redacted]
Joint pain,[a] post-activity	[redacted]	[redacted]	[redacted]	[redacted]
Joint pain,[a] pre- vs. post-	[redacted]	[redacted]	[redacted]	[redacted]
Joint stiffness[a]	[redacted]	[redacted]	[redacted]	[redacted]
Physical energy,[b] patient	[redacted]	[redacted]	[redacted]	[redacted]
Physical energy,[b] parent	[redacted]	[redacted]	[redacted]	[redacted]
Shoulder ROM, active flexion (°)[c]	[redacted]	[redacted]	[redacted]	[redacted]
ROM, passive flexion (°)	[redacted]	[redacted]	[redacted]	[redacted]
ROM, active extension (°)	[redacted]	[redacted]	[redacted]	[redacted]
ROM, passive extension (°)	[redacted]	[redacted]	[redacted]	[redacted]
ROM, active lateral rotation (°)	[redacted]	[redacted]	[redacted]	[redacted]
ROM, passive lateral rotation (°)	[redacted]	[redacted]	[redacted]	[redacted]
Coin pick-up (number of coins)	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

ROM = range of motion; SD = standard deviation; vs. = versus.

TABLE 26: JOINT PAIN, RANGE OF MOTION, AND COIN PICK-UP AT WEEK 24

End Point	Galsulfase		Placebo		Mean Difference ± SE (Galsulfase — Placebo)	*P* value
	n	Change at Week 24 (Mean ± SE)	n	Change at Week 24 (Mean ± SE)		
Joint pain,[a] pre-activity	[redacted]					
Joint pain,[a] post-activity						
Joint pain,[a] pre- vs. post-						
Joint stiffness[a]						
Physical energy,[b] patient						
Physical energy,[b] parent						
ROM, passive flexion (°)						
ROM, active extension (°)						
ROM, passive extension (°)						
ROM, active lateral rotation (°)						
ROM, passive lateral rotation (°)						
Coin pick-up (number of coins)						

[redacted]

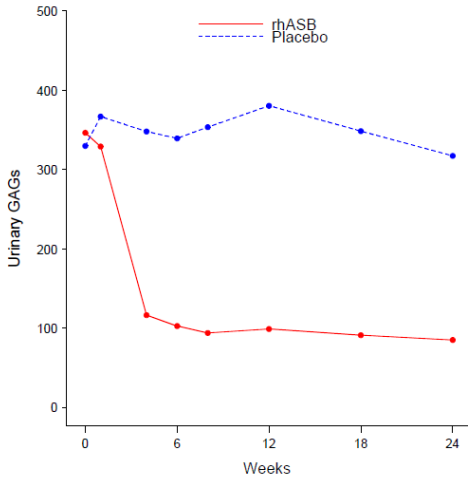
SE = standard error; vs. = versus.

TABLE 27: URINARY GLYCOSAMINOGLYCAN: SUMMARY OF MEANS OVER TIME

	Observed (Raw) Data (mcg/mg Creatinine)							
	Galsulfase			Placebo			Difference	
	n	Mean	SD	n	Mean	SD	Mean	SE
Baseline	19	346	128	20	330	114	17	39
Week 1	18	329	131	19	367	134	–38	43
Week 4	19	116	48	20	348	126	–232	30
Week 6	19	103	45	19	339	95	–237	24
Week 8	19	94	47	19	354	107	–260	27
Week 12	19	99	52	19	381	218	–282	51
Week 18	19	91	44	19	349	199	–258	47
Week 24	19	85	35	19	317	80	–232	20

SD = standard deviation; SE = standard error.
Source: Clinical Study Report, p. 90.

FIGURE 3: OBSERVED MEANS OF URINARY GLYCOSAMINOGLYCAN OVER TIME



GAG = glycosaminoglycan; rhASB = recombinant human *N*-acetylgalactosamine-4-sulfatase (galsulfase).
Source: Clinical Study Report, p. 89.

TABLE 28: ANALYSIS OF VARIANCE AND ADDITIONAL ANALYSES: URINARY GLYCOSAMINOGLYCAN (24 WEEKS)

Method	Mean ± SE (Galsulfase — Placebo)	95% CI	*P* value
ANOVA	[redacted]	[redacted]	[redacted]
T-test on the difference from baseline	[redacted]	[redacted]	[redacted]
Wilcoxon test on the difference from baseline	[redacted]	[redacted]	[redacted]

[redacted]

ANOVA = analysis of variance; CI = confidence interval; SE = standard error.

TABLE 29: NUMBER OF RESPONDERS IN URINARY GLYCOSAMINOGLYCAN

	Observed Data	
	Galsulfase	Placebo
	N = 19	N = 20
Responders,[a] n/N (%)		
All sites	[redacted]	[redacted]
Fisher's exact test:[b] $P \leq 0.001$	[redacted]	
At each site		
US	[redacted]	[redacted]
Germany	[redacted]	[redacted]
England	[redacted]	[redacted]
Brazil	[redacted]	[redacted]
France	[redacted]	[redacted]
Portugal	[redacted]	[redacted]

[redacted]

TABLE 30: SUMMARY OF PATIENTS EXPERIENCING ADVERSE EVENTS DURING TREATMENT

Category	Galsulfase (N = 19)	Placebo (N = 20)
	Number of Patients (%)	
Patients experiencing > 0 AEs	[redacted]	[redacted]
Patients with any AE (%) occurring during infusion	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
WDAE	[redacted]	[redacted]
Patients with SAEs	[redacted]	[redacted]
IARs	[redacted]	[redacted]

[redacted]

AE = adverse event; IAR = infusion-associated reaction; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

TABLE 31: ADVERSE EVENTS

	Galsulfase (N = 19)	Placebo (N = 20)
	Number of Patients (%)	
All	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Ear pain	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
Influenza-like illness	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Ear infection	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]
Restrictive pulmonary disease	[redacted]	[redacted]
Hernia pain	[redacted]	[redacted]
Infusion site pain	[redacted]	[redacted]
Abdominal distention	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Hordeolum	[redacted]	[redacted]
Furuncle	[redacted]	[redacted]
Sleep apnea syndrome	[redacted]	[redacted]
Obstructive airways disorder	[redacted]	[redacted]
Poor venous access	[redacted]	[redacted]
Anemia	[redacted]	[redacted]
Post-procedural pain	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]

	Galsulfase (N = 19)	Placebo (N = 20)
	Number of Patients (%)	
Splenomegaly	[redacted]	[redacted]
Hepatomegaly	[redacted]	[redacted]
Hepatosplenomegaly	[redacted]	[redacted]
Tracheotomy	[redacted]	[redacted]

[redacted]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the available evidence on the validity of the following outcome measures:

- Six-minute walk test (6MWT) and 12-minute walk test (12MWT)
- Three-minute stair climb test (3MSCT)
- Urinary glycosaminoglycan (GAG).

Findings

Six-minute walk test and 12-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, whereas the 12MWT prolongs the evaluation to 12 minutes.[17] The American Thoracic Society (ATS) provides guidelines for the standardization of this test in order to maximize reliability.[17] Walk tests aim to evaluate global function of organ systems involved in exercise — namely the heart, lungs, peripheral circulation, blood, nervous system, muscles, bones, and joints — during walking, a self-paced activity.[17] Patients with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) (MPS VI) may have decreased walk distance from numerous disease-related factors, including stunted growth, cardiac valve dysfunction, impaired lung function, and bone and joint deformities.[6]

A literature search was conducted to identify validation studies of the 6MWT and 12MWT in MPS VI and other mucopolysaccharidosis (MPS) conditions; none were identified. Walk tests were originally developed to primarily evaluate cardiopulmonary function in cardiac and pulmonary conditions (e.g., chronic obstructive pulmonary disease [COPD], heart failure, pulmonary hypertension), but studies have been performed to validate these tests in musculoskeletal conditions such as fibromyalgia.[17]

No minimal clinically important difference (MCID) has been identified or proposed in MPS VI. MCIDs for distances reported for other conditions, such as COPD (43 m) and heart failure (54 m), do not necessarily generalize to MPS VI given key differences between patient populations. Patients with MPS VI are typically much younger than patients with COPD or heart failure, and have functional impairment, primarily from musculoskeletal as well as cardiopulmonary causes.[17,18] A search for validation of the 6MWT in other rheumatological or musculoskeletal conditions yielded one small study in patients with systemic sclerosis, which failed to find a correlation between 6MWT abnormalities with disease severity or health assessment questionnaire scores.[30]

Key limitations of these walk tests, especially in pediatric patients, include a learning effect with repeated testing; the confounding effect of patient motivation, encouragement, and cooperation; and the impact of age, height, and weight on walking distance.[17] The learning effect could result in performance and detection bias (i.e., false-positive apparent benefits) when evaluating an intervention using these walk tests in a non-blinded, uncontrolled study. Additionally, differences in patient motivation, encouragement, and cooperation between assessments can affect walking distance by a similar magnitude as the effect of interventions,[31] which can produce substantial variability and be a source of performance bias in a non-blinded, uncontrolled study. Finally, previous studies have identified that age, height, and weight affect distance travelled in six minutes,[32,33] which may affect 6MWT results obtained from trials of longer duration. An additional consideration in trials of MPS VI, which often presents with stunted growth, is that an intervention could theoretically improve 6MWT by increasing or restoring growth without affecting other determinants of function, or vice versa.

Notably, the FDA agreed to the use of 12MWT as an acceptable primary efficacy outcome for MPS VI in the design phase of ASB-03-05,[12] and the 6MWT was accepted by the FDA as a primary efficacy outcome for other MPS disorders. Specifically, the FDA considered the 12MWT to be a clinical end point, one that directly measures the functional limitations relevant to the daily living of patients with MPS VI, and indirectly measures the cardiovascular, respiratory and joint manifestations of the disease. However, it was not viewed by the agency as a surrogate for clinical benefits in terms of substantial morbidity or mortality.

Three-minute stair climb test

The 3MSCT is another test of global function; it evaluates the number of steps climbed, allowing for use of handrails and rest periods, over three minutes.[18] A search for validation studies of the 3MSCT test in MPS VI and other MPS conditions identified none. No MCID has been proposed in MPS VI, and no MCID value was identified in the literature for other conditions. The 3MSCT correlates strongly with other measures of endurance, such as the 12MWT. Limitations for the 3MSCT are similar to those of the 6MWT and 12MWT.

Urinary glycosaminoglycan

MPS VI is characterized by impairment in the enzymatic degradation of a GAG called dermatan sulfate, resulting in accumulation and clinical manifestations. As there is impairment in the degradation of this GAG, there can be a detectable rise in urinary GAGs, because the kidneys serve as an alternate elimination pathway. Presence of elevated urinary dermatan sulfate is used to aid in the diagnosis of MPS VI (although it cannot provide definitive diagnosis of the condition), and total urinary GAG is also used for monitoring of disease activity. Urinary GAGs are measured from the first morning void and normalized to urinary creatinine levels.

One cross-sectional study evaluated the correlation between total urinary GAGs and disease activity in MPS VI.[34] These investigators reported an association between high urinary GAG values (> 200 mcg/mg creatinine) and greater disease activity — as determined by shorter age-adjusted stature and body weight, worse 6MWT, decreased pulmonary function tests, and reduced joint range of motion (ROM) — but did not report estimates of correlation or association. No studies have identified an ideal or target urinary GAG value or demonstrated a clear association between urinary GAG value changes and long-term clinically important outcomes. Notably, urinary GAG values can be falsely negative in patients with MPS VI with obvious sequelae of the disease.[6]

Summary

No studies to validate 6MWT, 12MWT, or 3MSCT in MPS VI or any other MPS disorder were identified. The lack of validation studies and an MCID for these outcomes, and the numerous external factors that can affect performance, limit the value of these outcomes for evaluating the efficacy of interventions for MPS VI, although 12MWT was accepted by the FDA as a direct measure of functional limitation in trials of MPS VI. Similarly, urinary GAG is a surrogate outcome with biological plausibility but insufficient evidence of an association with MPS VI disease activity or clinically important outcomes.

Given the rare presentation of MPS VI, 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 VI is perhaps not surprising. However, it does impair the ability to judge the effectiveness of treatments such as galsulfase.

APPENDIX 6: SUMMARY OF OTHER STUDIES

Aim

To summarize the findings of the extension study (ASB-03-06) of the pivotal phase 3 trial (ASB-03-05) of galsulfase.[12,13,16,28]

Findings

Study objectives and baseline disease characteristics

Study ASB-03-06 was a phase 3 multi-centre, international, open-label extension trial of all patients who completed the 24-week double-blind (DB) portion of ASB-03-05. The objective of this extension study was to assess long-term efficacy and harms of galsulfase in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) (MPS VI). A 12-minute walk test (12MWT) and three-minute walk test (3MSCT) were measured at weeks 36 and 48, and then at 48-week intervals thereafter, and at study completion.[12,13] Urinary glycosaminoglycans (GAGs) were measured at 12-week intervals throughout the study. Additional pre-defined efficacy outcomes measured during this phase included shoulder range of motion (ROM), coin pick-up test, joint pain, joint stiffness, physical energy level, cardiac function (electrocardiogram and echocardiogram) and respiratory function tests, and visual examination at week 48.[12,13]

Thirty-eight patients completing the 24-week DB randomized controlled trial (RCT) (ASB-03-05) from both the galsulfase (N = 19) and placebo groups (N= 19) received open-label galsulfase 1 mg/kg of body weight intravenous (IV) weekly for the duration of follow-up.

Results

Available reports described all efficacy data up to 72 weeks of open-label galsulfase (i.e., week 96 from start of ASB-03-05) and safety data up to 135 weeks of open-label galsulfase (i.e., week 159 from start of ASB-03-05) separately for patients who initially received galsulfase and placebo in ASB-03-05 (Table 32 and Table 33).[28]

Efficacy

Table 32 summarizes the efficacy data for ASB-03-06. In patients who received galsulfase in the DB trial, measures of endurance tended to remain stable or improve during the extension study. During ASB-03-05, patients receiving placebo had minimal change from baseline in measures of endurance. These patients had statistically significant improvements from both start and end of ASB-03-05 upon initiating galsulfase in the extension study that were sustained to week 96.

Urinary GAG levels decreased significantly upon initiation of galsulfase and remained stable during continued administration. There were minimal, statistically non-significant changes in all other efficacy outcomes, consistent with findings from ASB-03-05.

TABLE 32: EFFICACY OUTCOMES DURING ASB-03-06 ([redacted])

	Placebo — Galsulfase				Galsulfase — Galsulfase			
	Baseline of ASB-03-05	Week 24 of ASB-03-05	[redacted]	[redacted]	Baseline of ASB-03-05	Week 24 of ASB-03-05	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
12MWT, m								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3MSCT, stairs/min								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3MSCT = three-minute stair climb test; 12MWT = 12-minute walk test; ASB = arylsulfatase B (*N*-acetylgalactosamine-4-sulfatase); SD = standard deviation.

Harms

Table 33 summarizes safety data from ASB-03-06. All 38 patients received at least one dose of galsulfase and were included in the analysis of safety. All patients experienced at least one adverse effect and approximately half of patients experienced a serious adverse event (SAE). Various types of SAEs were observed, and all were attributed to complications of MPS VI rather than galsulfase treatment; none were infusion-related.

TABLE 33: SAFETY OUTCOMES DURING ASB-03-06 (UP TO WEEK 135)

Outcome	Placebo — Galsulfase	Galsulfase — Galsulfase
n	19	19
AEs		
Number of patients (%)	19 (100)	19 (100)
Number of events	884	942
SAEs		
Number of patients (%)	9 (47)	10 (53)
Number of events	22	12
WDAEs, n	0	0
Deaths, n	0	0
IAR during infusion		
Number of patients (%)	13 (68%)	13 (68%)
Number of events	70	194

AE = adverse event; ASB = arylsulfatase B (N-acetylgalactosamine-4-sulfatase); IAR = infusion-associated reaction; SAE = serious adverse event; WDAE = withdrawal due to adverse effect.

Limitation

The primary limitations of this extension study, as with the DB trial, are the small sample size and uncertain validity and clinical relevance of the efficacy outcomes. Secondly, the non-randomized, open-label design is prone to performance, detection, and expectation bias, and the lack of a placebo control group prevents estimation of the magnitude of effect associated with long-term galsulfase therapy compared with best supportive care. However, the efficacy results demonstrate consistency with the primary findings of ASB-03-05, and the safety data do not suggest any additional long-term concerns beyond those reported in the original DB trial.

Summary

In this 135-week extension trial of ASB-03-05, patients with MPS VI treated with galsulfase appeared to maintain the endurance gains demonstrated in the original RCT. Additionally, galsulfase demonstrated a safety profile consistent with the RCT.

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