

**Drug Profile**

**Elosulfase Alfa (BMN 110) for the Treatment of Mucopolysaccharidosis IVA (Morquio A Syndrome)**

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## **Abstract**

**Introduction:** Morquio A syndrome is a rare, autosomal recessive, lysosomal storage disorder caused by a deficiency in the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS). In 2014, the use of recombinant human GALNS, elosulfase alfa, was approved in Europe, Canada, the United States, Australia, and Brazil for the treatment of Morquio A syndrome. Elosulfase alfa is administered intravenously once-weekly at a dose of 2.0 mg/kg.

**Areas Covered:** This is a review of the efficacy, safety and tolerability, pharmacokinetics and pharmacodynamics, and other outcomes of elosulfase alfa treatment of patients with Morquio A. A discussion of other treatment considerations, limitations, and future directions in the use of elosulfase alfa is provided.

**Expert Commentary:** Pharmacokinetic studies outside of clinical trials and in “real-world” clinical settings need to be performed. We cannot currently predict which patient is going to respond well to enzyme replacement therapy; thus, all patients should be given the option to receive treatment for at least 12 months. Additionally, accurate biomarkers for evaluating disease state and drug responsiveness would greatly aid in the treatment of patients with Morquio A. In addition, improved and innovative daily lifestyle measures are greatly needed to adequately measure clinical response and true impact on quality of life.

**Keywords:** elosulfase alfa, enzyme replacement therapy, GALNS, lysosomal storage disorder, Morquio A, MPS IVA, mucopolysaccharidosis

## 1. Introduction

Mucopolysaccharidosis IVA (also referred to as MPS IVA, Morquio A syndrome, Morquio-Brailsford syndrome, or OMIM 253000) is a rare, autosomal recessive, lysosomal storage disorder caused by a deficiency in the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS; EC 3.1.6.4). The deficiency in GALNS results in the impaired degradation and subsequent accumulation of the glycosaminoglycans (GAGs), keratan sulfate and chondroitin-6-sulfate in the tissues, bones, and major organs [1-4].

The *GALNS* gene, found on chromosome 16q24 [5], is approximately 50 kb, and contains 14 exons with 2339 base pairs; it encodes a 522-amino acid enzyme. Mutations of *GALNS* are numerous, heterogeneous, and can occur throughout the coding sequence. As of June 2016 according to the *GALNS* Mutation Database, there are 368 known variants of the *GALNS* gene of which 278 are pathogenic or likely pathogenic, 74 are of unknown clinical significance, and 16 are benign [6].

The point prevalence of Morquio A syndrome has been reported as 1 per 323,000 (Denmark), 1 per 599,000 (United Kingdom), 1 per 926,000 (Australia), and 1 per 1,872,000 (Malaysia) [7]. The birth prevalence of Morquio A using the recommended diagnostic methods ranges from 1 per 71,000 in the United Arab Emirates to 1 per 500,000 in Japan. MPS IVA affects approximately 3000 people in the developed world and has therefore been designated as an orphan disease [8].

Persons with Morquio A syndrome may appear healthy at birth. Abnormalities present at birth may be recognized by experts; however, the majority of patients begin to develop multi-organ signs and symptoms of the disease that catch the attention even of non-rare disease clinicians by as early as 6 months of age.

Morquio A syndrome was first described in 1929 by Dr. Luis Morquio, a pediatric physician from Uruguay [9], and by Dr. James Brailsford, an English radiologist [10] from Birmingham, United Kingdom; therefore, the disease is sometimes called Morquio-Brailsford syndrome. In his publication (written in

French), Dr. Morquio described a Swedish family of 4 siblings who exhibited corneal clouding, aortic valve disease, and high levels of urinary keratan sulfate (uKS).

Signs and symptoms exhibited by patients with Morquio A include, but are not limited to, short stature for the particular age with a short neck; abnormal skeletal development and spinal deformities; joint hypermobility and laxity; genu valgum (or knock knees); large elbows and wrists; waddling gait; bell-shaped chest; deficiency in tooth enamel; abnormal heart development, including aortic valve disease; respiratory compromise, including airway obstruction; corneal clouding; hearing impairment; mild hepatosplenomegaly. Deficient enzyme activity has been detected as early as the first trimester [11]; the resultant abnormal GAG excretion has also been noted in utero [12]. In contrast to most MPS disorders, Morquio A is not known to have brain involvement or to cause significant cognitive impairment. Minor abnormalities have been described, but the exact significance on cognitive development is unknown at present [13,14]. Morquio A results in a diverse range of clinical manifestations. The wide spectrum of disease progression (ie, severe/classical, intermediate, and mild/attenuated) among individuals with MPS IVA is likely due to the high degree of genetic heterogeneity. While some persons may die during childhood, others with milder “non-classical/attenuated” forms of the disorder may live longer and have a life expectancy that is near normal [15,16]. In one study by Lavery and colleagues in the United Kingdom, respiratory failure was the primary cause of death in nearly two-thirds of patients (63%) with Morquio A [17]. Other causes of death included cardiac failure (11%), post-traumatic organ failure (11%), complications of surgery (11%), and myocardial infarction (4%).

## **2. Diagnosis of Morquio A**

The initial suspicion of Morquio A syndrome is based on the appearance of symptoms described above, but because of heterogeneous expression, it is not always easy to differentiate from other disorders and there may be a substantial delay between the development of symptoms and diagnosis [14]. By 2 to 3 years of age, there tends to be sufficient GAG accumulation in the tissues, bones, and organs to indicate the presence of a disorder. During a screening test, which may provide false-negatives especially in older patients as there is a natural decline in uKS levels with age, high uKS may be observed [18] but age-appropriate reference ranges should be used. A definitive diagnosis of Morquio A syndrome is made when low GALNS activity in leukocytes and fibroblasts is observed [14,18]. Molecular testing is used to confirm the diagnosis.

## **3. Management of Morquio A**

Historically, there has been no approved treatment for Morquio A, and thus the disorder has been managed by supportive measures including symptom-based medication, physical therapy, rehabilitation, and surgery [14]. Orthopedic surgical procedures of the spine and upper and lower limbs, including hip and/or knee replacement are often performed in these patients [14,19,20]. Common procedures include surgery to decompress and fuse the bones of the upper neck to the base of the skull to prevent destabilization of the cervical vertebrae and potential damage to the spinal cord due to spinal stenosis and cervical instability caused by ligamentous laxity, odontoid hypoplasia, and/or atlantoaxial instability [21-24]. Procedures that involve anesthesia and airway support have also been studied because patients with Morquio A who undergo surgical procedures present with challenging compounding factors, including difficulty establishing and maintaining airway control due to previous cervical spinal fusions, abnormal neck and chest anatomy, and deposition of GAGs in the airway tissues [25].

Hematopoietic stem cell transplantation (HSCT) has been tried in an effort to provide a source of normal enzyme for Morquio A patients and remains under investigation [19,20,25,26]. HSCT is known to carry a high risk of adverse events (AEs), including graft-versus-host-disease and a high risk for mortality caused by infection [19,25] and has not been formally evaluated as part of a controlled clinical study. In a 2012 report by the Agency for Healthcare Research and Quality (Rockville, MD, USA) on the status of HSCT for childhood diseases, it was concluded that the body of evidence on HSCT and Morquio A was insufficient to draw conclusions [27]. Additionally, as in other MPS disorders, HSCT has not been shown to effectively treat the severe skeletal manifestations of Morquio A [25]; this is likely due to lower vascularization of bone tissue. In a more recent paper by Yabe and colleagues, HSCT was shown to yield significant long-term improvements in quality of life (QOL) for Morquio A patients [26]. Investigators followed 4 patients for over 10 years after HSCT and reported that “the levels of the enzyme activity in the recipients’ lymphocytes reached the levels of donors’ enzyme activities within 2 years after HSCT.” For the successive over 10 years post-bone marrow transplantation, GALNS activity in lymphocytes was maintained at the same level as the donors. However, the clinical relevance of this finding is unknown. With the exception of 1 patient who had an osteotomy in both legs 1 year after bone marrow transplantation, 3 other recipients had no orthopedic surgical intervention. All cases remained ambulatory—3 patients could walk over 400 m and activities of daily living (ADL) for patients with HSCT were better than for untreated patients. A patient who underwent HSCT at 4 years of age showed the best ADL score [26]. The authors concluded that “the long-term study of HSCT has demonstrated therapeutic effect in slowing of progression of the disease in respiratory function, ADL, and biochemical findings, suggesting that HSCT is a therapeutic option for patients with Morquio A.” While promising, more studies of HSCT are needed with a larger study population before any definitive conclusions for its efficacy in treating Morquio A can be made. Post-mortem histology findings have been reported in a post-HSCT Morquio A patient in which the bone marrow transplant had failed. At the time of death,

significant abnormality was present in all tissues [28].

#### **4. Elosulfase alfa for the treatment of Morquio A**

Elosulfase alfa (Vimizim<sup>®</sup>, BioMarin Pharmaceutical Inc., San Rafael, CA, USA) is a recombinant human GALNS (rhGALNS) produced in Chinese hamster ovarian cells expressing the cDNA for human GALNS and was developed to be used as enzyme replacement therapy (ERT) for the treatment of Morquio A [2]. Elosulfase alfa is harvested from conditioned media from Chinese hamster ovarian cells that overexpress GALNS and sulfatase modifying factor 1, which encodes the formylglycine-generating enzyme that activates all sulfatases [29]. The purification recovery of rhGALNS is about 56%, and the harvested enzyme has a specific activity of about 2 U/mg. Identical to human GALNS in amino acid sequence and N-linked glycosylation sites, rhGALNS has an average molecular weight of 55 kDa [2]. Recombinant human GALNS associates as a non-covalent dimer in solution, is stable in serum with an extrapolated half-life of about 200 hours at pH 7.4, and exhibits affinity for hydroxyapatite, the major mineral constituent of bone [29]. The phosphorylated oligosaccharide profile of rhGALNS suggests the capacity for uptake and internalization by the mannose-6-phosphate receptor system on lysosomes.

#### **5. Pharmacokinetics of elosulfase alfa**

The pharmacokinetics of elosulfase alfa from the pivotal phase 3 trial [2] were reported by Qi and colleagues in 2014 [30]. Analysis of pharmacokinetics was done during and after the initial infusion of elosulfase alfa and was repeated during and after the week 22 elosulfase alfa infusion (**Figure 1**). Blood samples were taken before and at 15, 60, and 120 minutes after beginning the infusion, and at 5, 15, 30, 60, 120, and 180 minutes after the completion of the infusion. Pharmacokinetic parameters were estimated by non-compartment analysis using WinNonlin<sup>®</sup> (Certara, L.P., Princeton, NJ, USA) software. The half-life of elosulfase alfa in plasma increased from approximately 7 minutes after the initial infusion



to approximately 36 minutes after repeated administration over 22 weeks (**Table 1**) [30]. Notably, the intracellular half-life of elosulfase alfa is estimated to be 5 to 7 days (as determined *in vitro* in human Morquio A fibroblasts) [15]. The increase in plasma half-life appeared to be associated with the appearance of neutralizing anti-elosulfase alfa antibodies in the majority of patients [30]. Total exposure as assessed by  $AUC_{0-last}$ , also increased over 22 weeks of administration by 181% or 192%. This apparent increase in exposure did not appear to influence pharmacodynamics, efficacy, or safety outcomes in patients.

## **6. Pharmacodynamics of elosulfase alfa**

Elosulfase alfa is transported into lysosomes via a mannose-6-phosphate-mediated mechanism where it acts to replace and normalize the levels of the deficient endogenous enzyme [29]. In preclinical and clinical studies, the major pharmacodynamic effect is the reduction in uKS due to the increased lysosomal degradation of this metabolite [29,31]. In preclinical studies, elosulfase alfa administered intravenously to wild-type mice resulted in biodistribution throughout all the layers of the heart, the entire thickness of the growth plate, and in macrophages and hepatocytes [29].

## **7. Findings from clinical studies of elosulfase alfa**

### *7.1 Overview of clinical study program to date*

To provide context for the subsequent elosulfase alfa studies, the natural history of Morquio A was captured in the Morquio A Clinical Assessment Program (MorCAP) [32,33]. The first clinical study performed for elosulfase alfa was a phase 1/2 dose escalation study in pediatric patients over the age of 5 years [31]. This study was followed by the phase 3 pivotal trial which, unlike the phase 1/2 trial, included adult as well as pediatric patients and was restricted to only those walking  $\geq 30$  and  $\leq 325$  meters in the 6-minute walk test (6MWT), the primary efficacy endpoint, to ensure that all patients

could complete the assessment and that all patients were impaired enough at baseline to show improvement with treatment [2,34]. An open-label extension study followed the pivotal trial and, in the absence of a placebo group, natural history data from MorCAP were used for comparisons [35]. Due to the exclusion of patients under 5 years of age and those unable to walk at least 30 meters in the 6MWT, 2 additional studies were undertaken for these sub-populations. Both were phase 2, open-label studies. The first evaluated patients  $\geq 5$  years of age with limited ambulation (unable to walk  $\geq 30$  meters in the 6MWT) using a variety of alternative assessments [36]. The second evaluated patients under 5 years of age, focused on safety and tolerability, and utilized uKS and growth velocity as efficacy measures [37]. An additional pilot study evaluated a higher dose of elosulfase alfa in the Morquio A population  $\geq 7$  years of age and able to walk  $\geq 200$  meters in the 6MWT [38]. These inclusion criteria were selected in order to enroll a population of subjects who were able to perform a cardio-pulmonary exercise test of sufficient duration to provide useful information on cardio-pulmonary/exercise capacity.

#### *7. 2 Phase 1/2 study in children ages 5 to 18*

In a phase 1/2 dose escalation study of 20 patients between the ages of 5 and 18 years, patients were given elosulfase alfa at 0.1, 1.0, and 2.0 mg/kg/week for 3 consecutive 12-week periods, followed by a 36- to 48-week continuation study at 1.0 mg/kg/week (**Table 2**). Of the 20 patients enrolled, 17 continued into an extension study and were dosed at 2.0 mg/kg/week [31]. While elosulfase alfa was well tolerated, most study patients experienced drug-related AEs that were mild to moderate in severity and not treatment-limiting. One patient had a serious reaction on the 0.1 mg/kg/week dosage and withdrew from the study, while another patient who did not complete all infusions due to infusion-associated reactions (IARs) discontinued the study during the continuation phase. Decreased uKS levels were observed; the lowest levels were observed at the 2.0 mg/kg/week dose in both the dose escalation

study and the extension study, supporting the use of 2.0 mg/kg/week as the standard dose for treatment in the subsequent phase 3 clinical trial.

### *7.3 Phase 3 clinical trial in patients ages 5 to 57*

In the pivotal, randomized, multicenter, double-blind, placebo-controlled, phase 3 clinical trial of 176 patients with Morquio A, patients were administered elosulfase alfa either 2.0 mg/kg/week or 2.0 mg/kg every other week, or placebo [2]. Patients received premedication with an antihistamine approximately 30–60 minutes prior to the start of elosulfase alfa infusion [2,34]. At the physician's discretion, patients could receive additional agents including corticosteroids, a sedating antihistamine, H2 blockers, or montelukast sodium to reduce IARs. Elosulfase alfa was diluted to a final volume of either 100 or 250 mL with saline solution, allowed to reach room temperature, and administered intravenously. Infusions were administered over approximately 4 hours.

After only 24 weeks, patients randomized to 2.0 mg/kg/week saw a significant ( $p=0.0174$ ) improvement in the 6MWT compared with patients randomized to placebo (**Table 3**) [2]. However, there was no improvement in the 6MWT when elosulfase alfa was administered at a dose of 2.0 mg/kg every other week. A summary table of the phase 3 trial results are shown in **Table 3**. Elosulfase alfa treatment had no effect on the number of stairs climbed in the 3-minute stair climb test (3MSCT) over the initial 24-week study period; there was however, a reduction in uKS by 40.7%. The study also showed numerical improvements over placebo after 24 weeks of treatment with elosulfase alfa 2.0 mg/kg/week for maximum voluntary ventilation (MVV;  $p=0.094$ ) and forced vital capacity (FVC;  $p=0.304$ ) [14].

A subsequent multi-domain analysis of the pivotal phase 3 trial used a composite measure developed by Delphi strategy (based on an equal weighting of the change from baseline to week 24 of the z-scores of 6MWT, 3MSCT, and MVV) to determine if composite measure components were

clinically meaningful [39]. The composite measure indicated that there was a substantial improvement on 1, 2, or 3 variables within 24 weeks of treatment (**Figure 2**) [14,39]. An O'Brien rank-sum test was performed post-hoc as a prespecified supportive analysis of the composite endpoint [39]. The O'Brien rank-sum test allows the statistical evaluation of multiple endpoints non-parametrically; it is less sensitive to outliers and deviations from a normal distribution found in parametric tests. Patients were ranked on each component of the composite endpoint (ie, 6MWT, 3MSCT, MVV, height z-scores, and the 3 domains of the MPS-Health Assessment Questionnaire [MPS-HAQ]), and the score for each patient was obtained as the sum of the ranks. Evaluated composite endpoints included various combinations with and without the 6MWT results to assess whether efficacy was 6MWT-dependent or if there was evidence of efficacy of other variables besides 6MWT. A forest plot (**Figure 3**) was created to depict the impact of elosulfase alfa treatment on patient 6MWT, 3MSCT, MVV, and other measures of respiratory function as well as MPS-HAQ. The variables 6MWT, 3MSCT, forced expiratory time, forced expiratory volume in 1 second (FEV<sub>1</sub>), FVC, MVV, growth rate, height z-score, MPS-HAQ Caregiver Assistance domain, and MPS-HAQ Mobility domain all showed improvement upon treatment with elosulfase alfa (**Figure 3**) [39]. These findings support the belief that the 6MWT is currently the best measure for assessment of the efficacy of elosulfase alfa in a clinical trial, yet 6MWT does not fully capture the impact of treatment for patients with Morquio A syndrome. A comprehensive way to assess patients with the disorder has not yet been described, but any method should assess multiple or composite outcomes rather than a single outcome.

What is true for Duchenne muscular dystrophy and 6MWT may possibly hold true for Morquio A. In a paper published in 2013, Henricson and colleagues were able to show that in Duchenne muscular dystrophy, 6MWT correlated strongly with Pediatric Outcomes Data Collection Instrument (PODCI) global and transfer/mobility scores. Essentially, PODCI scales were predictive of 6MWT performance. Therefore the paper states that "a 'meaningful' 4.5 point change in a low PODCI transfer/ basic mobility

score from 30.0 to 34.5 was associated with a 5.6m 6MWD change from 150.3 to 155.9. At PODCI levels closer to normative levels for healthy controls, the change in 6MWD distance associated with a ‘meaningful’ change in PODCI scores was almost 46m.” The authors concluded that “at lower levels of function, smaller increases in 6MWD result in meaningful change in QOL instrument scores” and “at higher levels of function, larger increases may be necessary to achieve the same QOL change score.” [40]. Perhaps a parallel concept of clinically meaningful changes could be applied to 6MWT in some Morquio A patients. In the pivotal elosulfase alfa study, Harmatz and colleagues [39] reported a mean baseline 6MWT value of 203.9 (76.3) meters for the patients randomized to weekly treatment. Perhaps the improved level of endurance they achieved after treatment (243.3 [83.5] meters) may have more clinical meaning to the QOL of some patients than simply numerical improvement in meters walked in total.

### *7.3. Safety and tolerability*

Elosulfase alfa treatment was generally well tolerated in all reported clinical trials. The most frequent AEs were mild to moderate IARs, such as vomiting, pyrexia, and headache. IARs occurred in 91.5% of patients treated with placebo versus 89.7% with elosulfase alfa 2.0 mg/kg/week [2] in the pivotal study. Hypersensitivity AEs occurred in 11.9% of patients who received placebo during the trial versus 20.7% of patients treated with elosulfase alfa 2.0 mg/kg/week. Of the 1345 total infusions administered during the 24-week trial, only 17 (1.3%) were interrupted (n=14) or discontinued (n=3) and required medical intervention. The majority of serious AEs (SAEs) were deemed to be either infusion-related, procedure-related, or Morquio A disease-related. Two patients in the weekly treated group experienced SAEs that appeared to be related to the study drug; however, neither SAE led to study discontinuation and no deaths occurred during the study.

#### 7.4. Immunogenicity

To evaluate elosulfase alfa immunogenicity, antibody positivity and titer were assessed throughout the trial. Serum samples for immunogenicity testing were collected at baseline and periodically throughout the 24 weeks of the study. If a patient experienced a severe IAR or an IAR requiring infusion cessation, additional blood samples were drawn for determination of immunoglobulin E (IgE). Samples may have also been taken at the investigator's discretion [34]. Titers of total elosulfase alfa-specific antibody (TAb) and neutralizing antibodies (NAb) were assessed. All patients treated with elosulfase alfa developed anti-elosulfase alfa antibodies. The mean TAb titers increased with time and then levels were maintained between weeks 16 and 24. Approximately 20% of all patients (n=36/176) tested positive for TAb against elosulfase alfa at baseline. A total of 87% (n=48/55) of patients receiving elosulfase alfa at 2.0 mg/kg/week tested positive for NAb at week 24. In contrast, a total of 8.6% (n=5/58) of those patients tested positive for elosulfase alfa-specific IgE. There was no consistent correlation between severe hypersensitivity AEs and mean TAb titers, nor was there a clear correlation between hypersensitivity and NAb positivity. Additionally, the presence or absence of TAb at baseline did not correlate with the incidence or maximum severity of hypersensitivity AEs.

The 3 patients who presented with serious drug-related AEs of hypersensitivity, vomiting, and anaphylactic reaction did not test positive for antidrug IgE at any time during the study [34]. Patients who were positive for antidrug IgE did not have any reported severe hypersensitivity AEs. Lastly, patients with higher TAb titers or higher NAb positivity rates did not have reduced 6MWT results compared with patients with lower antibody responses. The relatively high incidence of positive antidrug antibody at baseline and in both the treatment and placebo cohorts is likely related to the conservative cut-point of the assay, designed to reduce the possibility of false-negative results. Rather, this may have resulted in an assay that was overly sensitive and gave false-positives.

### *7.5 Long-term effects on endurance, safety, and respiratory function*

A recently published phase 3 extension study investigated 120 weeks of total treatment with elosulfase alfa [35]. During this extension study, patients initially received elosulfase alfa 2.0 mg/kg/week (n=85) or 2.0 mg/kg/every other week (n=88), prior to establishment of 2.0 mg/kg/week as the recommended dose, at which point all patients (n=173) received 2.0 mg/kg weekly. From pre-treatment baseline, an improvement and subsequent stabilization were observed in 6MWT and 3MSCT; 6MWT and 3MSCT were significantly improved over the gradual decline seen in corresponding subpopulations of untreated patients from the MorCAP natural history study [32,33]. Initial endurance improvements were maintained regardless of the endurance capacity of patients at baseline, use of a walking aid, and age [35]. Long-term treatment with elosulfase alfa 2.0 mg/kg/week resulted in sustained reduction of uKS levels. The safety profile of elosulfase alfa in patients with Morquio A was consistent with the phase 3 study with no new AEs identified. The most commonly reported AEs overall were mild to moderate IARs, which were found to be generally manageable by symptomatic treatment and/or modification of the infusion rate.

The long-term effects (up to a total of 120 weeks) of elosulfase alfa treatment on respiratory function have also been studied [41]. The respiratory function efficacy evaluations conducted in this extension study were identical to those conducted during the 24-week pivotal trial, which have been described in detail previously [2]. Respiratory function was assessed as one of the measures of long-term efficacy, and tests included FVC, FEV<sub>1</sub>, and MVV. These tests were performed every 24 weeks in phase 1 of the study and every 48 weeks in phase 2 [41]. Again, due to the long-term nature of this study, a placebo group was not included; instead, respiratory function data from a comparable untreated patient population from the multi-center, cross-sectional MorCAP natural history study [32,33], were used to place the results in the context of a progressive disease. The study found that MVV improved up to week 72 and then stabilized. FVC and FEV<sub>1</sub> increased continuously over 120 weeks

(mean increases for patients treated was 9.2% for FVC, 8.8% for FEV<sub>1</sub>, and 6.1% for MVV after 120 weeks). In patients under age 14 years, both treated and untreated patients showed improvements, presumptively due to growth (elosulfase alfa-treated patients had a mean (standard error [SE]) change in height of +5.1 (3.5) cm compared with +2.8 (2.8) cm in the untreated natural control patients; however, the improvements in respiratory function were greater in treated patients.

Treated patients over 14 years of age showed an improvement in respiratory function while deterioration occurred in untreated patients of similar age. Height changes for these older patients were minimal regardless of treatment with mean changes (SE) in height of +1.3 (3.2) cm in the treated patients and -0.0 (0.9) cm in the untreated natural history subjects [41]. Furthermore, in the younger patients, improvements in FVC were correlated with increases in height; however, in the older patients, no correlation was evident.

This long-term study suggests that ERT with elosulfase alfa slows down, and partially reverses, the natural progression of respiratory dysfunction associated with Morquio A over a 2-year period [41]. ERT-induced growth acceleration may contribute considerably to this effect in younger patients; however, it is likely that other mechanisms that are related to decreasing GAG accumulation may also play a role in older patients.

#### *7.6 A study of limited ambulation*

Efficacy and safety of elosulfase alfa ERT were assessed in an open-label, phase 2, multi-national study in 15 patients with Morquio A older than 5 years of age who were also unable to walk more than 30 m in the 6MWT [36]. Patients received elosulfase alfa 2.0 mg/kg/week intravenously for 48 weeks. Primary efficacy measures were the Functional Dexterity Test (FDT), pinch/grip strength, mobility in a modified timed 25-foot walk (T25FW), pain, and QOL. Secondary efficacy measures were respiratory function and uKS; safety/tolerability was also assessed. In all, 15 patients received elosulfase alfa; 10



completed treatment through 48 weeks and received  $\geq 80\%$  of planned infusions. Mean FDT speed showed a trend toward improvement over 48 weeks, mainly in the dominant hand. The mean (SE) number of pegs/minute for the dominant hand was 15.4 (3.5) at baseline. Mean (SE) change from baseline to week 48 was 1.4 (3.1) pegs/minute. However, the improvement in FDT speed was largely caused by 1 patient who had an improvement of 22 pegs/minute. Of the 9 patients who were able to perform the FDT at baseline, 4 showed an improvement in FDT speed over 48 weeks of  $\geq 1$  peg/minute, 2 were stable, and 2 showed a decrease of  $\geq 1$  peg/minute.

Upper extremity function was also assessed by grip and pinch strength tests. Unfortunately, most patients had difficulty performing these tests according to the study protocol due to weak grip, hypermobile wrists, and/or short stature (ie, patients were unable to put their feet on the floor), leading to differences in test execution among centers. Regardless of test execution methods, grip and pinch strength remained unchanged over the course of the study [36].

Mean (SE) speed in the T25FW at baseline was 22.9 (10.3) feet/minute [36]. In several cases, the T25FW was not performed either at the discretion of the investigator and/or for patients with significant pain. The 6 out of 10 patients who performed the T25FW at both baseline and at later visits, used different ambulation methods: 3 patients walked (1 with the assistance of a walking device), 1 walked on his knees, 1 crawled, and 1 used her arms only. Although the variability among patients was high due to the different methods of test execution, all 4 patients who completed the assessment both at baseline and week 48 showed an improvement in speed (feet/minute) resulting in a mean (SE) change from baseline of 75 (47) %.

Overall, FVC and FEV<sub>1</sub> remained relatively stable and MVV increased slightly over 48 weeks [36]. Five of 10 patients reported virtually no pain (score  $\leq 2$  on the pain intensity/severity scale) at baseline; 2 children reported pain intensity scores of 5.3 and 5.5, corresponding to medium pain; 3 adult patients had pain intensity scores ranging from 3–7 and reported considerable pain interference with walking

ability (pain interference scores 5–10). Due to small sample sizes, the use of different assessment devices in children and adults, and high variability among patients, meaningful collective analysis of data is difficult. Individual patient data showed a reduction in pain intensity/severity (>1 point) over 48 weeks in 2 of the 5 patients with pain at baseline (score >3 on the pain intensity/severity scale); 1 patient also stopped using non-steroidal topical analgesics during the study. However, pain became more severe in 2 out of 10 patients.

Overall, this study highlighted the importance of evaluating the impact of elosulfase alfa on an individual basis—particularly for severely affected Morquio A patients—because benefits of treatment manifest differently from one patient to the next.

#### *7.7 Phase 2 clinical trial in children under age 5*

In a separate phase 2 trial of 15 patients under the age of 5 years, elosulfase alfa was found to be well tolerated and produced a decrease in uKS; there was also a trend toward increased growth [37]. All 15 patients reported at least 1 AE with the most common drug-related AEs being pyrexia (40%) and vomiting (33%); most AEs were mild to moderate in severity. All 15 patients also reported at least 1 infusion-related AE, which were also mild to moderate in severity. All infusion-related AEs were manageable with treatment for symptoms including oxygen supplementation; intravenous steroids, antihistamines, and/or fluid management; or adjustment of the infusion rate.

#### *7.8 Pilot study of 2 doses of elosulfase alfa*

In a randomized, double-blind, uncontrolled pilot study, patients with Morquio A able to walk  $\geq 200$  meters in the 6MWT were given 1 of 2 doses of elosulfase alfa—2.0 mg/kg/week or a higher dose of 4.0 mg/kg/week [38]. The study evaluated the effects of the 2 doses on 6MWT, 3MSCT,

pharmacokinetic parameters, and uKS levels. Exercise capacity and various possible physiological contributors to endurance such as cardiac function, respiratory function, and pain were assessed as well.

Levels of uKS decreased considerably from baseline after treatment in both dose groups, reaching similar mean and median absolute levels [38]. However, no meaningful changes from baseline in 6MWT distance were observed in either dose group. The lack of impact in the 6MWT may be due to the inclusion criteria, which was designed to recruit a study population healthy enough to complete the cardio-pulmonary exercise test, muscle strength tests, and other efficacy measures. Notably, mean baseline walking distance was 372 meters, which was considerably more than the values of around 200 meters observed in the phase 3 study. Numerical improvements were observed for 3MSCT at 4.0 mg/kg/week but not 2.0 mg/kg/week. It is possible that the lack of improvement at the lower dose may be the result of a “ceiling effect.” Additional endpoints evaluated for the pooled study population (exercise capacity, muscle strength, respiratory function, and pain) also showed trends toward improvement with treatment.

The mean  $t_{1/2}$  was approximately 6 minutes at week 0 for both dosing groups and increased to 23.2 and 31.1 min at week 23 for the 2.0 and 4.0 mg/kg/week dose groups, respectively [38]. Following repeat dosing,  $AUC_{0-t}$  and  $C_{max}$  increased by 48% and 44%, respectively, at week 23 compared with week 0 for the 2.0 mg/kg/week dose group; and by 69% and 100%, respectively, for the 4.0 mg/kg/week dose group. Differences between the 2.0 and 4.0 mg/kg/week doses in the mean  $AUC_{0-t}$  and  $C_{max}$  were greater than dose proportionately, which indicates that the pharmacokinetics of elosulfase alfa are not linear over this dose range. Evaluation of pharmacokinetic versus pharmacodynamics and efficacy data showed a positive relationship between elosulfase alfa exposure ( $AUC_{0-t}$  and  $C_{max}$ ) at week 23 and uKS % change from week 0 to week 24. A positive correlation was also found with changes in the 3MSCT but not with changes in the 6MWT or MVV.

Safety results were similar for both doses and were in line with what was previously reported in the primary study [38]. All drug-related AEs were mild to moderate in severity. Similar to previous reports, all patients developed anti-elosulfase alfa TABs and NABs during the study, which mostly remained positive for the duration of the study, but no relation between antibody titers and endurance outcomes, uKS changes, or hypersensitivity reactions were observed.

This recent study gives us additional safety and tolerability data on the approved dose of elosulfase alfa (2.0 mg/kg/week) as well as on a higher dose (4.0 mg/kg/week) in patients with Morquio A [38]. In addition, this is the first report to comprehensively explore aspects of exercise capacity, muscle strength, and pain in patients with Morquio A, providing new insights into the physiology and symptomatology of this disease.

#### *7.9 Assessment of potential biomarkers*

Accurate biomarkers for evaluating disease state and drug responsiveness are needed [42,43]. Biomarkers are objective indications of medical state observed from outside the patient, which can be measured accurately and reproducibly [44]. Martell and colleagues performed a study of 88 candidate biomarkers to monitor disease progression and treatment responsiveness in patients with Morquio A [42]. Levels of 88 candidate biomarkers were compared in plasma samples from 50 healthy controls and 78 patients with Morquio A who were not receiving ERT to test for significant correlations to the presence of Morquio A. Morquio A samples were also tested for correlations between candidate biomarkers and age, endurance, or uKS levels. Then, levels of the same 88 analytes were followed over 36 weeks in 20 patients with Morquio A who were receiving ERT to test for significant correlations related to ERT, age, or endurance. The investigators found that 19 candidate biomarkers were significantly different between Morquio A and healthy individuals. Of these, 5 candidate biomarkers also changed significantly in response to ERT. These were alpha-1-antitrypsin, eotaxin, lipoprotein (a), matrix

metalloprotein-2, and serum amyloid P. Three of these—alpha-1-antitrypsin, lipoprotein (a), and serum amyloid P—were significantly lower in individuals with Morquio A syndrome versus healthy individuals and were increased during ERT. The authors concluded that the candidate biomarkers alpha-1-antitrypsin, lipoprotein (a), and serum amyloid P may be suitable biomarkers, in addition to uKS, to follow the response to ERT in patients with Morquio A, although further investigations are warranted.

A systems biology approach using genome-scale human metabolic reconstruction has been studied by Salazar and colleagues in an effort to discover additional biomarkers for MPS [43]. Investigators used *in silico* MPS models to predict changes in metabolic profiles; then evaluated those candidate biomarkers *in vivo* to see if they correlated with the *in silico* prediction. Beta-hexosaminidase and  $\beta$ -glucuronidase were identified as 2 potential biomarkers for Morquio A. Beta-hexosaminidase was assayed in human MPS IVA skin fibroblasts, while  $\beta$ -glucuronidase and  $\beta$ -hexosaminidase activity was assayed in leukocytes from a patient with Morquio A. Beta-hexosaminidase activity was significantly lower in MPS IVA skin fibroblasts than the levels seen in normal skin fibroblasts, while  $\beta$ -glucuronidase activity in MPS IVA leukocytes was reduced about 40% of the levels observed in normal leukocytes.

## **8. Regulatory affairs**

The use of the ERT, elosulfase alfa, is approved in the European Union, Canada, the United States, Australia, Brazil, Japan, and Mexico for the treatment of Morquio A syndrome [8,37]. Elosulfase alfa is administered once-weekly at a dose of 2.0 mg/kg, intravenously [2].

## **9. Expert commentary**

Pharmacokinetic studies outside of clinical trials and in “real-world” clinical settings need to be performed. High immunogenicity of the drug is a confounding factor in the consideration of treatment with elosulfase alfa. The antibody assays may be overly sensitive and may provide an over-

representation of the incidence of an antibody response. Importantly, immunogenicity does not appear to correlate with the efficacy of elosulfase alfa. While high immunogenicity has been reported in only a few patients [34], some clinicians continue to be concerned with the drug's immunological risk, particularly in the belief that the presence of antibodies directed against elosulfase alfa may increase the risk of IAR and infusion-site reactions. However, no correlation between immune response and IAR or infusion-site reactions has been shown, and in clinical trials a small minority of patients were observed to have elevated immune responses.

We cannot currently predict which patient is going to respond well to ERT [47]. In clinical practice, about 10% of patients are “super responders” who respond beyond all expectations. However there also appears to be a small group that never responds to ERT. In between these extremes lies the core group that responds as expected. Because we cannot currently predict responders versus non-responders, patients who have Morquio A and are receiving elosulfase alfa should be treated for at least 12 months before assessing response to the drug.

However, benefits to patients are not adequately captured in QOL assessments [36]. In the recently published limited ambulation study, patients with Morquio A showed improvement after treatment with elosulfase alfa in personally significant ways such as with 1 patient who after treatment was able to type on a computer, reach behind her head, and drink from a cup. Another patient reported dramatic improvements in sleep, breathing, and energy level. Yet another patient who was not previously able to lie flat on his back due to breathing problems found that this was improved while being treated with elosulfase alfa. A female patient showed improved functional ability by being able to comb her hair and speak more clearly and understandably. Unfortunately, while a patient's 6MWT and respiratory volumes may have moderately changed (or not at all), patients and their caregivers individually report that they feel less fatigued and have made physical activity gains and significant improvements on an individual level. Although patients and their caregivers or family members report

these daily changes to be significant to them, to date we have not been able to adequately capture and report such individual improvements through current standardized assessments of QOL.

To adequately measure clinical response, improved and more innovative daily lifestyle measures are greatly needed. Lifestyle trackers that document and provide an around-the-clock record of activity and sleep habits may hold some promise for the future [48-54]. However, we have yet to effectively capture and document those daily lifestyle effects and changes that are more significant for patients with Morquio A.

It should be noted that in the United Kingdom and Canada, most patients are infused at home. In the United States, patients are infused in infusion centers, which increases costs for an already costly drug. However, patients infused at infusion centers may receive other benefits such as emotional support from other patients, families, and healthcare workers. Regardless of the setting, it is important that clinicians and healthcare providers—including infusion nurses—are well trained in administering ERT, ensuring the proper and effective rate of infusion as well as drug dose, and performing measures to prevent adverse reactions to treatment.

Elosulfase alfa has been shown to be effective at increasing the distance patients can walk and improving respiratory function. There is still much to learn and improve upon in our knowledge of Morquio A syndrome and its treatment. Before elosulfase alfa, there was no approved drug for Morquio A—management of symptoms was the only recourse. However, now we have hope for the future in this field.

## **10. Five-year view**

Targeted therapies to increase the effectiveness of ERT have been discussed [19,45]. Pre-clinical research into gene-targeted therapy has shown some promise in treating Morquio A [19,45,46]. In the future, a small, specific, targeted molecule in addition to ERT to address issues of immunogenicity and

bone uptake may be more effective [19,45]. The next 5 years hold the promise that we will likely be better at predicting which mutations in *GALNS* indicate which patients will be more or less responsive to ERT. The actual mechanism of action of elosulfase alfa is currently unknown and requires further study. However, we now understand that Morquio A is a multi-organ disorder—and not just skeletal—and that ERT effectively improves patient endurance, pulmonary function, and QOL.



## 11. Key Issues

- Elosulfase alfa is approved in the European Union, Canada, the United States, Australia, Mexico, Japan, and Brazil for the treatment of Morquio A syndrome
- Elosulfase alfa (2.0 mg/kg/week) results in a significant improvement in 6MWT in patients with Morquio A and has been shown in the long-term to improve both endurance and respiratory function
- Elosulfase alfa is generally well-tolerated
- Because we cannot currently predict which patient is going to respond well to ERT, all patients should be given the option to receive treatment for at least 12 months
- Accurate biomarkers for evaluating disease state and drug responsiveness would greatly aid in the treatment of patients with Morquio A
- In addition, improved and innovative daily lifestyle measures are greatly needed to adequately measure clinical response and true impact on QOL

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## Declaration of Interest

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**Abbreviations:**

3MSCT, 3-minute stair climb test

6MWT, 6-minute walk test

ADL, activities of daily living

AE(s), adverse event(s)

AUC, area under the curve

cDNA, complementary DNA

ERT, enzyme replacement therapy

FDT, Functional Dexterity Test

FEV<sub>1</sub>, forced expiratory volume in 1 second

FVC, forced vital capacity

GAG, glycosaminoglycan

GALNS, N-acetylgalactosamine-6-sulfatase HSCT, hematopoietic stem cell transplantation

IAR(s), infusion-associated reaction(s)

IgE, immunoglobulin E

MorCAP, Morquio A Clinical Assessment Program MPS, mucopolysaccharidosis

MPS-HAQ, MPS-Health Assessment Questionnaire MVV, maximum voluntary ventilation

NAb, neutralizing antibodies

PODCI, Pediatric Outcomes Data Collection Instrument

QOL, quality of life

QOW, once every 2 weeks

QW, once per week

rhGALNS, recombinant human GALNS

SAE(s), serious AE(s)

SE, standard error

TAb, total elosulfase alfa-specific antibody

T25FW, timed 25-foot walk

uKS, urinary keratan sulfate

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\*-Papers of interest

\*\*\_Papers of particular interest

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**Table 1.** Pharmacokinetic parameters for elosulfase alfa in patients with Morquio A syndrome. Table adapted and used with permission from Qi et al, 2014 [30].

	Dosage	
	2.0 mg/kg QOW	2.0 mg/kg QW
<b>Week 0</b>		
n	24	22
C <sub>max</sub> , ng/mL	1438 ± 435	1494 ± 534
t <sub>max</sub> , min	150 ± 58	172 ± 75
AUC <sub>0-last</sub> , ng•min/mL	248,720 ± 97,064	237,884 ± 100,329
AUC <sub>0-∞</sub> , ng•min/mL	287,597 ± 96,432 (n=14)	231,074 ± 103,207
t <sub>1/2</sub> , min	6.6 ± 3.1 (n=14)	(n=15) 7.5 ± 5.5 (n=15)
CL, mL/min/kg	7.5 ± 2.0 (n=14)	10.0 ± 3.7 (n=15)
V <sub>ss</sub> , mL/kg	219 ± 95 (n=12)	396 ± 316 (n=14)
V <sub>z</sub> , mL/kg	69 ± 34 (n=14)	124 ± 144 (n=15)
<b>Week 22</b>		
n	23	22
C <sub>max</sub> , ng/mL	2616 ± 2702	4036 ± 3237
t <sub>max</sub> , min	159 ± 61	202 ± 91
AUC <sub>0-last</sub> , ng•min/mL	411,687 ± 420,280	577,371 ± 416,317
AUC <sub>0-∞</sub> , ng•min/mL	463,460 ± 491,419	619,080 ± 422,048 (n=20)
t <sub>1/2</sub> , min	(n=19) 19.3 ± 19.2 (n=19)	35.9 ± 21.5 (n=20)
CL, mL/min/kg	6.5 ± 2.9 (n=19)	7.1 ± 13.0 (n=20)
V <sub>ss</sub> , mL/kg	245 ± 273 (n=17)	650 ± 1,842 (n=20)
V <sub>z</sub> , mL/kg	120 ± 71 (n=19)	300 ± 543 (n=20)

Values expressed as mean ± standard deviation. For some patients, t<sub>1/2</sub>, CL, V<sub>ss</sub>, and V<sub>z</sub> could not be estimated due to insufficient data in the terminal phase of the plasma profile. The number of patients whose data was used for these calculation is indicated in parentheses. AUC<sub>0-last</sub>, area under the plasma concentration-time curve from the start of infusion to the last measureable observation; CL, total clearance of drug after intravenous administration; C<sub>max</sub>, maximum observed concentration; t<sub>max</sub>, time of observed C<sub>max</sub>; t<sub>1/2</sub>, plasma elimination half-life; V<sub>ss</sub>, apparent volume of distribution at steady state; V<sub>z</sub>, apparent volume of distribution based upon the terminal phase t<sub>1/2</sub>.

**Table 2.** Summary of phase 1/2 studies.

	Study				
	MOR-002	MOR-100	MOR-006	MOR-007	MOR-008
Study design	OL, dose escalation	OL, extension study of MOR-002	Harmatz et al, 2016 [36] OL	Jones et al, 2015 [37] OL	Burton et al, 2015 [38] R, DB, Pilot study
Study phase	1/2	1/2	2	2	2
Timeline	Prior to drug approval	Prior to drug approval	Post-drug approval	Post-drug approval	Post-drug approval
Patients	5–18 years old	5–18 years old	≥5 years old with limited ambulation	<5 years old	≥7 years old who could walk ≥200 m on 6MWT
Dosage (N)	0.1 (N=20), 1.0 (n=18), 2.0 (n=18) mg/kg/week	2.0 mg/kg/week (N=17)	2.0 mg/kg/week (N=15)	2.0 mg/kg/week (N=15)	2.0 mg/kg/week (n=10) or 4.0 mg/kg/week (n=5; randomized in a 2:1 ratio)
Treatment duration	36 weeks during dose escalation followed by 36 weeks at 1.0 mg/kg/week (followed by an extension study [MOR-100] at 2.0 mg/kg/week)	Extension study up to an additional 192 weeks	48 weeks followed by extension study up to 96 weeks	52 weeks (primary treatment phase) Extension phase up to an additional 156 weeks	27 weeks (primary treatment phase), followed by an extension phase for up to 166 weeks (all 15 patients dosed at 2.0 mg/kg/week during extension)
Male:female	12:8	9:8	9:6	7:8	9:16
Age, median (min, max)	7.5 (4, 16)	7.5 (4.9, 16.1)	18.7 (9.8, 42.4)	3.1 (0.8, 4.9)	11.5 (7.8, 39.5)

Efficacy					
uKS (median)	-40.6% (at end of 2.0 mg/kg/week dose, week 36)	-36.4% (mean) at week 72 -58.9% (mean) at week 168	52.4% (mean) at week 48	-39.9% at week 26 -43.5% at week 52 (not in publication)	Week 24 2.0 group: -37.4% (mean) 4.0 group: -55.5% (mean)
Functional assessments	Trend toward improvement in 6MWT distance and 3MSCT	Improvement in 6MWT distance and sustained improvement in 3MSCT	Trend toward improved functional dexterity in dominant hands  Improvement in ambulation speed in patients able to perform test at baseline and follow-up  All other outcomes too variable to draw conclusions		No improvement in 6MWT distance was seen in either dose group during the primary treatment phase, possibly due to an assessment “ceiling effect” in this higher endurance population  Numerical improvement in the 3MSCT in the 4.0 mg/kg/week group at week 24, but not in the 2.0-mg/kg/week group
Safety	1 patient withdrew from the study during the 0.1-mg/kg/week phase due to a life-threatening type 1 hypersensitivity reaction. The patient’s sibling also withdrew at that time	No patients withdrew due to AEs  Study drug-related AEs were reported for 16 (94.1%) patients: pyrexia (41.2%), headache (29.4%), increased blood IgE (29.4%), and diarrhea	No patients withdrew due to AEs  Study drug-related AEs were reported for 13 (86.7%) patients: headache (40.0%), nausea, pyrexia, vomiting (20.0% each)	No patients withdrew due to AEs  All patients developed antibodies to elosulfase alfa by 4 weeks  11 patients (73.3%) experienced at least 1	No patients withdrew due to AEs  Over the 27-week primary phase of the study, the most common study drug-related AEs in the 2.0 mg/kg/week group were: headache

<p>All evaluable patients developed elosulfase alfa antibodies by Week 18 with generally sustained and increasing titers during the 72-week treatment period</p>	<p>(23.5%) All evaluable patients developed elosulfase alfa antibodies during MOR-002 by Week 18</p>	<p>All treated subjects developed elosulfase alfa antibodies by 4 weeks</p>	<p>drug-related AE: pyrexia (40%) and vomiting (33.3%) were most common</p>	<p>(46.7%), pyrexia (40.0%), vomiting (33.3%), and nausea (33.3%)</p>
<p>There was no apparent relationship between total antibody titer and efficacy and safety outcomes</p>	<p>Positivity was sustained until Week 192</p> <p>There was no apparent relationship between total antibody titer and efficacy and safety outcomes</p>	<p>Due to the exploratory nature of the efficacy assessments performed in this study and the low sample numbers, no analysis was performed to determine the relationship between immunogenicity and efficacy outcomes</p>	<p>All patients experienced at least 1 infusion-associated reaction</p> <p>All patients developed antibodies to elosulfase alfa and levels were sustained by Week 51</p>	<p>The most common study drug-related AEs in the 4.0 mg/kg group were: headache, pyrexia, abdominal pain, cough, dizziness, fatigue, and nausea (all 20%)</p>
			<p>No apparent relationship was observed between total antibody titers and safety or height z-score measurements</p>	<p>All 2.0 mg/kg/week and 4.0 mg/kg/week treated patients tested positive for total antibodies to elosulfase alfa by Week 6 and remained positive for the duration of the study</p>
				<p>No consistent associations were evident between immunogenicity and efficacy outcomes</p>

3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; AE, adverse event; DB, double-blind; OL, open-label; R, randomized; SF-36, Short Form-36.

**Table 3.** Summary of the effect of elosulfase alfa treatment on primary, secondary, and tertiary endpoints in the pivotal Morquio A phase 3 clinical trial. Table adapted and used with permission from Hendriksz et al, 2014 [2].

Treatment effect	Dosage	
	2.0 mg/kg/QOW vs Placebo (N=59 vs 59)	2.0 mg/kg/week vs Placebo (N=58 vs 59)
<b>Primary outcome</b>		
6MWT distance (m changes from baseline)		
LS Mean difference (95% CI)	0.5 (-17.8, 18.9)	22.5 (4.0, 40.9)
<i>p</i> -value	0.954	0.017
<b>Secondary outcome</b>		
3MSCT (stairs/min change from baseline)		
LS mean difference (95% CI)	-0.5 (-3.7, 2.8)	1.1 (-2.1, 4.4)
<i>p</i> -value	0.778	0.494
Normalized uKS (% change from baseline)		
LS mean difference (95% CI)	-30.2 (-38.5, -22.0)	-40.7 (-49.0, -32.4)
<b>Tertiary outcomes</b>		
MVV (% change from baseline)		
LS mean difference (95% CI)	3.4 (-9.9, 16.6)	10.3 (-1.8, 22.4)
6MWT/3MSCT/MVV composite z-score (change from baseline)		
LS mean difference (95% CI)	0.0 (-0.1, 0.2)	0.1 (-0.0, 0.3)
FVC (% change from baseline)		
LS mean difference (95% CI)	3.0 (-2.4, 8.3)	3.3 (-3.1, 9.6)
FEV <sub>1</sub> (% change from baseline)		
LS mean difference (95% CI)	0.2 (-7.4, 7.9)	1.8 (-5.5, 9.2)
MPS-HAQ (decreasing scores reflect functional improvement)		
Self-care domain score (change from baseline)		
LS mean difference (95% CI)	-0.1 (-0.5, 0.3)	-0.1 (-0.5, 0.3)
Caregiver assistance domain score (change from baseline)		
LS mean difference (95% CI)	-0.4 (-2.4, 1.6)	-0.9 (-2.8, 1.1)

Mobility domain score (change from baseline)		
LS mean difference (95% CI)	-0.3 (-0.8, 0.2)	-0.3 (-0.8, 0.3)
<b>Anthropometric measures</b>		
Standing height z-score (change from baseline)		
LS mean difference (95% CI)	0.1 (-0.1, 0.3)	0.1 (-0.0, 0.3)
Growth rate z-score (change from baseline)		
LS mean difference (95% CI)	0.4 (-0.1, 0.9)	0.4 (-0.1, 0.9)

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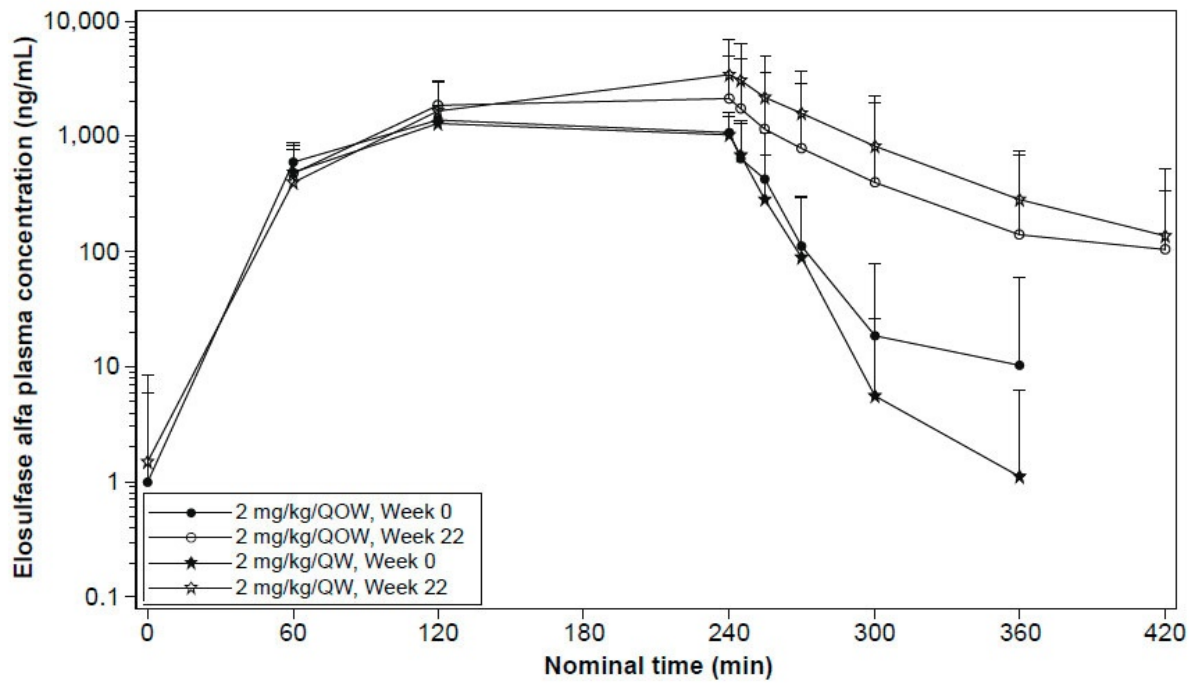
3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; LS,

least squares; MPS-HAQ, mucopolysaccharidosis health assessment questionnaire; MVV, maximal voluntary ventilation; QOW, every other week; uKS, urinary

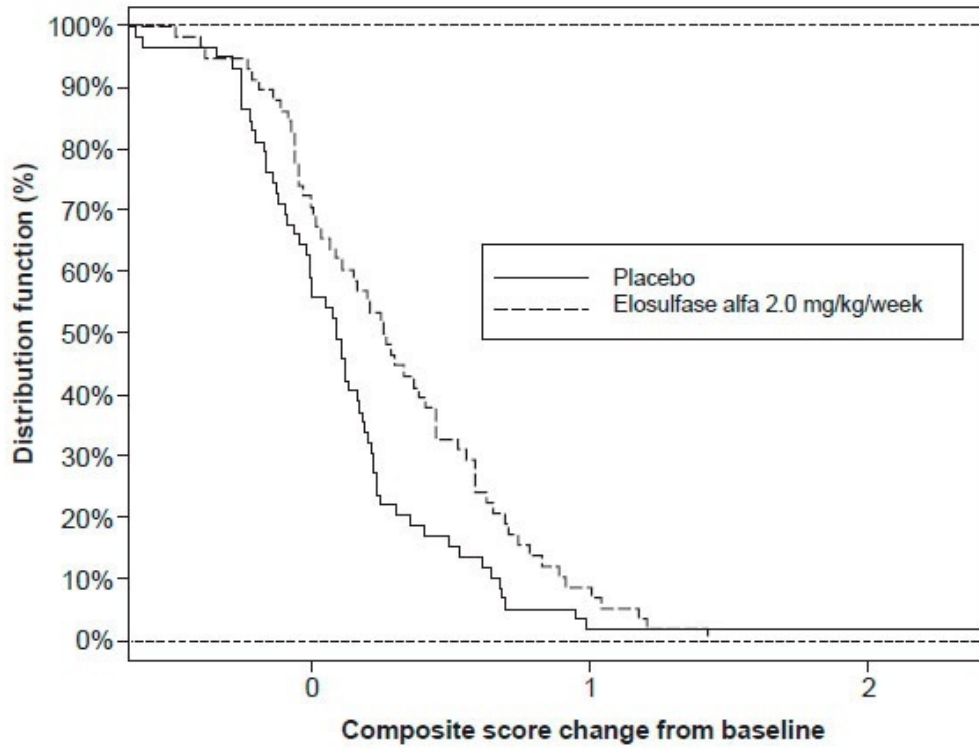
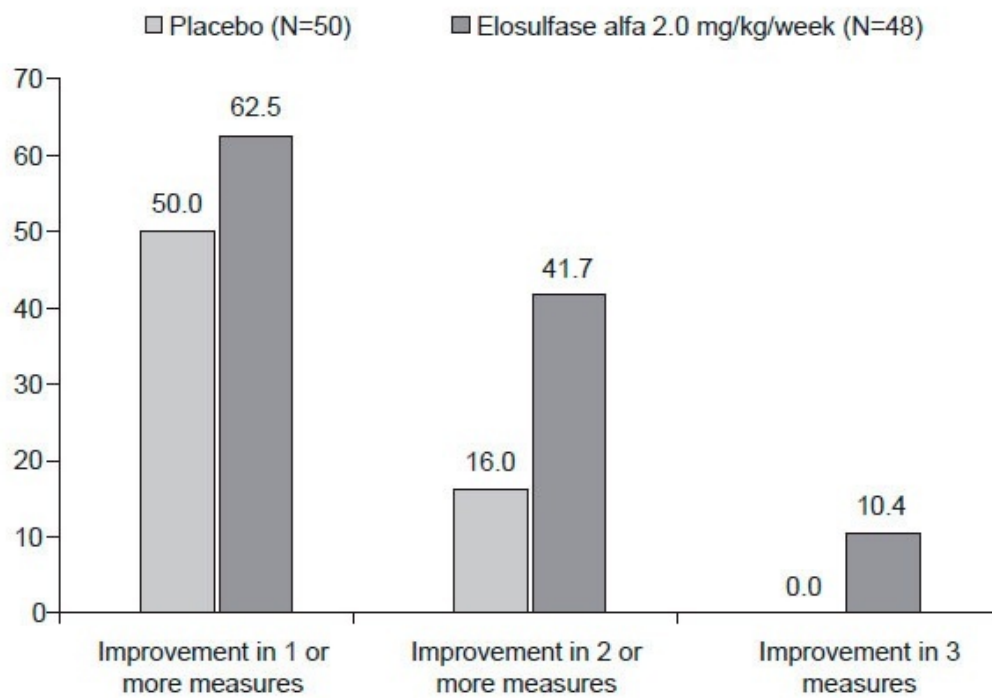
keratan sulfate



**Figure 1.** Mean plasma concentration profiles of elosulfase alfa during and after infusion. QOW, once every 2 weeks; QW, once per week. Figure adapted and used with permission from Qi et al, 2014 [30].



**Figure 2.** (A) Responder analysis of primary composite score: cumulative distribution for change from baseline at week 24 (intent-to-treat [ITT] population). The composite scores were based on the average of the 24-week changes from baseline in normalized 6MWT, 3MSCT, and MVV components (z-scores). The percentage of subjects showing an improvement in the composite score at week 24 (as compared with baseline) was plotted against the continuous range of responses. Thus, the cumulative distribution function shows a continuous plot of the proportion of subjects at each point along the continuum of change in the measure. Negative responses indicate worsening in the composite score. (B) Delphi threshold responder analysis for 6MWT, 3MSCT, and MVV (ITT population, observed case). The graph displays the proportion of patients in the placebo and elosulfase alfa 2.0 mg/kg/week groups showing treatment response (according to Delphi panel recommendations) for at least 1, at least 2, or all 3 variables. Consensus recommendations for the responder definition threshold, expressed as the percent change improvement from baseline after 24 weeks of treatment, were at 15% change for the 6MWT, a 20% change from the 3MSCT, and a 20% change for MVV. Figure used with permission from Hendriksz et al, 2015 [39].

**A****B**

**Figure 3.** Summary of treatment effect of elosulfase alfa 2.0 mg/kg/week (QW) versus placebo (PBO) on efficacy endpoints (intent-to-treat population). The X-axis indicates estimates that were standardized to a common scale of measurement by dividing the estimate and confidence interval (CI) bounds for each endpoint by the standard error of that estimate. 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; FET, forced expiratory time; FEV<sub>1</sub>, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; MPS-HAQ, MPS-Health Assessment Questionnaire; MVV, maximum voluntary ventilation; PBO, placebo; QW, once per week. Figure used with permission from Hendriksz et al, 2015 [39].

