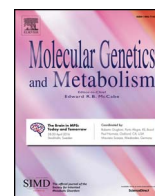




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# Safety, immunogenicity, and clinical outcomes in patients with Morquio A syndrome participating in 2 sequential open-label studies of elosulfase alfa enzyme replacement therapy (MOR-002/MOR-100), representing 5 years of treatment

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## ABSTRACT

Elosulfase alfa is an enzyme replacement therapy for Morquio A syndrome (mucopolysaccharidosis IVA), a multisystemic progressive lysosomal storage disorder. This report includes the primary treatment outcomes and immunogenicity profile of elosulfase alfa in patients with Morquio A syndrome from 2 sequential studies, MOR-002 ([ClinicalTrials.gov](https://clinicaltrials.gov/NCT00884949) NCT00884949) and MOR-100 (NCT01242111), representing > 5 years of clinical study data. MOR-002 was an open-label, single-arm phase 1/2 study that evaluated the pharmacokinetics, safety, immunogenicity, and preliminary efficacy of 3 sequential doses of elosulfase alfa (0.1, 1.0, and 2.0 mg/kg/week) in patients with Morquio A syndrome (n = 20) over 36 weeks, followed by an optional 36- to 48-week treatment period using elosulfase alfa 1.0 mg/kg once weekly (qw). During the 0.1 mg/kg dosing phase, 1 patient discontinued due to a type I hypersensitivity adverse event (AE), and that patient's sibling voluntarily discontinued in the absence of AEs. An additional patient discontinued due to recurrent infusion reactions during the 1.0 mg/kg continuation phase. The remaining 17 patients completed MOR-002 and enrolled in MOR-100, an open-label, long-term extension study that further evaluated safety and clinical outcomes with elosulfase alfa administered at 2.0 mg/kg qw. During the course of MOR-100, patients were given the option of receiving elosulfase alfa infusions at home with nursing assistance. Over the course of both studies, all patients experienced  $\geq 1$  AE and most patients experienced a drug-related AE, generally of mild or moderate severity. Hypersensitivity reactions reported as related to study drug occurred in 25% of patients. Thirteen patients who chose to receive infusions at home had the same tolerability and safety profile, as well as comparable compliance rates, as patients who chose to receive on-site infusions. All patients developed antibodies to elosulfase alfa. Positivity for neutralizing antibodies was associated with increased drug half-life and decreased drug clearance. Despite formation of anti-drug-binding (total antidrug antibodies, TAB) and in vitro neutralizing antibodies (NAb) in all patients, these types of immunogenicity to elosulfase alfa were not correlated with safety or clinical outcomes. In contrast with the reported natural history of Morquio A, no trends toward decreasing endurance, respiratory function, or ability to perform activities of daily living were observed in this cohort over the 5-year period.

**Abbreviations:** 3MSCT, 3-min stair climb test; 6MWT, 6-min walk test; AE, adverse event;  $AUC_{0-t}$ , area under the curve from time 0 to last measurable concentration;  $AUC_{inf}$ , area under the curve from time 0 to infinity; CI-M6PR, cation-independent mannose 6-phosphate receptor; CL, clearance;  $C_{max}$ , maximum observed concentration in plasma; ERT, enzyme replacement therapy; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GALNS, N-acetylgalactosamine-6-sulfatase; HAQ, Health Assessment Questionnaire; IgE, immunoglobulin E; IR, infusion reaction; IV, intravenous; KS, keratan sulfate; MedDRA, Medical Dictionary for Regulatory Activities; MorCAP, Morquio A Clinical Assessment Program; MPS, mucopolysaccharidosis; MVV, maximum voluntary ventilation; NAb, neutralizing antibodies; PD, pharmacodynamics; PK, pharmacokinetics; qw, once weekly; SAE, serious adverse event; SMQ, standardized MedDRA query;  $t_{1/2}$ , terminal half-life; TAB, total antibodies;  $T_{max}$ , time to reach  $C_{max}$ ; uKS, urine keratan sulfate;  $V_{dss}$ , volume of distribution at steady state;  $V_{dz}$ , volume of distribution based on the terminal rate constant

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## 1. Introduction

Morquio A syndrome (mucopolysaccharidosis [MPS] IVA; OMIM #253000) is a rare lysosomal storage disease caused by an autosomal recessive mutation in the gene encoding the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS; EC 3.1.6.4), which catalyzes the degradation of glycosaminoglycans, keratan sulfate (KS), and chondroitin-6-sulfate. The accumulation of glycosaminoglycans in the lysosome gives rise to a heterogeneous but progressive disorder. Clinical manifestations include skeletal dysplasia, cardiac and pulmonary compromise, short stature, pectus carinatum, spinal abnormalities, joint instability, corneal opacity, and impaired hearing [1–3]. This combination of symptoms gives rise to a progressive decline in functional abilities, including endurance. One natural history study has estimated progressive impairment of endurance at a rate of  $-4.86 \pm 3.25$  m per year in the 6-min walk test (6MWT) [1].

Elosulfase alfa (recombinant humanized GALNS; BMN 110; Vimizim®; BioMarin Pharmaceutical Inc., Novato, CA, USA) is an enzyme replacement therapy (ERT) approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of Morquio A syndrome. In MOR-004 (ClinicalTrials.gov NCT01275066), the pivotal 24-week randomized, placebo-controlled phase 3 clinical trial, intravenous elosulfase alfa 2.0 mg/kg once weekly (qw) demonstrated efficacy on the primary endpoint, the 6MWT. In the long-term extension study, MOR-005 (NCT01415427), elosulfase alfa demonstrated an acceptable safety profile at the 2.0 mg/kg qw dose over approximately 2 years, and mean improvements were reported for 6MWT distances [4], 3-min stair climb test (3MSCT) outcomes [4], and respiratory function (maximum voluntary ventilation [MVV], forced vital capacity [FVC], and forced expiratory volume in 1 s [FEV<sub>1</sub>]) [5]. The levels of the pharmacodynamic (PD) marker KS, which are elevated in the urine of patients with Morquio A syndrome, were significantly reduced during treatment with elosulfase alfa [4,6].

Preceding the pivotal phase 3 trial that led to approval, a 72- to 84-week phase 1/2 dose-finding trial (MOR-002; NCT00884949) was conducted in patients with Morquio A syndrome to identify the optimal efficacious dose of elosulfase alfa and assess its safety and tolerability. Following MOR-002, patients were invited to enroll in a long-term extension study (MOR-100; NCT01242111) to receive elosulfase alfa 2.0 mg/kg qw for an additional 192 weeks, which included its use as a home-infused therapy. This report describes the findings of the dose-escalation and long-term extension trials that together comprise 5 years of elosulfase alfa treatment outcomes in Morquio A syndrome.

## 2. Methods

### 2.1. Study design

MOR-002 was a multicenter, open-label, phase 1/2 clinical study designed to assess safety, dose, and preliminary efficacy of elosulfase alfa in individuals with Morquio A syndrome aged 5–18 years. To be eligible for enrollment, patients were required to have a diagnosis of MPS IVA based on reduced GALNS enzyme activity or confirmed by genetic testing. The dose-escalation period was 36 weeks, divided into 3 consecutive 12-week intervals, at doses of 0.1, 1.0, and 2.0 mg/kg qw. Weekly elosulfase alfa was administered intravenously (IV) over 4–5 h. Antihistamines were administered to patients before infusion as prophylaxis for potential hypersensitivity reactions. Patients who completed the dose-escalation period were eligible to enter the continuation period, receiving elosulfase alfa 1.0 mg/kg qw for an additional 36–48 weeks. Patients who completed MOR-002 were eligible to enter MOR-100, an optional long-term extension study evaluating 2.0 mg/kg qw elosulfase alfa treatment over 192 weeks.

In MOR-002 and at the start of MOR-100, all infusions were performed at study sites. However, following a protocol amendment, patients were given the option to continue receiving qw infusions in the

home setting, provided the treating physician deemed that home infusions were appropriate. Home health nurses met with the patient at his/her home and provided the same care as the study site, including pre-treatment with antihistamines and other agents as necessary and administration of study drug according to the same infusion rate schedule.

### 2.2. Pharmacokinetics and PD

Pharmacokinetic (PK) analysis was performed for samples collected at weeks 1, 12, 24, and 36 of MOR-002, and noncompartmental analyses were performed for elosulfase alfa 0.1 mg/kg qw, 1.0 mg/kg qw, and 2.0 mg/kg qw. The parameters measured were area under the curve from time 0 to last measurable concentration ( $AUC_{0-t}$ ) and time 0 to infinity ( $AUC_{inf}$ ), maximum observed concentration in plasma ( $C_{max}$ ) and time to reach  $C_{max}$  ( $T_{max}$ ), clearance (CL), volume of distribution based on the terminal rate constant ( $V_{d\alpha}$ ) and at steady state ( $V_{dss}$ ), and terminal half-life ( $t_{1/2}$ ) [7]. For determination of the PD effect of elosulfase alfa, urine KS (uKS) levels, normalized to creatinine levels, were measured at baseline and every 12 weeks for up to 72 weeks in the MOR-002 study and every 24 weeks for up to 168 weeks in the MOR-100 trial.

### 2.3. Clinical evaluation

Endurance was assessed using the 6MWT according to American Thoracic Society guidelines [8] and the 3MSCT [9]. Pulmonary function was assessed by FVC, FEV<sub>1</sub>, and MVV tests. Initially, these assessments were conducted at baseline, every 12 weeks for up to 72 weeks in MOR-002, and every 24 weeks up to 192 weeks in MOR-100. Following a protocol amendment implemented in the last year of the study, the frequency of the 6MWT, 3MSCT, and respiratory function tests was changed to every 48 weeks, and the frequency of weight measurements, physical examinations, clinical laboratory tests, pregnancy tests, uKS measurements, and creatinine tests was changed from every 12 weeks to every 24 weeks.

The intent-to-treat population consisted of all patients who enrolled in the study, including 2 patients who were unable to perform the 6MWT at baseline or during treatment: 1 due to physical reasons, who was imputed as 0 m, and the other, who could not perform the assessment for developmental reasons, was imputed as missing.

The MPS Health Assessment Questionnaire (MPS-HAQ) [2], a 52-item survey that assesses self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting), mobility skills (dexterity, mobility, walking, stair climbing, and gross motor skills), and the extent of required caregiver assistance in the performance of these activities was completed every 24 weeks. For patients < 14 years of age, the MPS-HAQ was completed by a parent or guardian.

### 2.4. Safety evaluation

The safety of elosulfase alfa in the MOR-002 study and the MOR-100 long-term extension was assessed by evaluating treatment-emergent adverse events (AEs) and changes in physical examination results (including neurological examinations and corneal clouding), vital signs, standard clinical laboratory tests (including serum chemistry, hematology, and urinalysis), cervical spine (flexion-extension) radiographs, electrocardiograms and echocardiograms, concomitant medications, and immunogenicity tests. AEs occurring after the onset of the infusion and within 1 day following the end of the infusion were considered to be temporally related to study drug infusion. These AEs were categorized by the following: did they occur during infusion, was the infusion interrupted or discontinued, and was medical intervention with IV steroids, IV antihistamines, IV fluids, or oxygen required. AEs were coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 and tabulated by system organ class, preferred term, and severity (Common Terminology Criteria for Adverse Events

criteria). Potential hypersensitivity AEs were identified using the broad anaphylactic reaction algorithmic standardized MedDRA query (SMQ) and the broad angioedema SMQ. Anaphylaxis events were reviewed against the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network 2006 criteria for anaphylaxis [10].

### 2.5. Immunogenicity testing

Serum samples, collected from patients at baseline and at weeks 3, 6, 9, 12, 18, 24, 30, 36, 48, 60, and 72 of MOR-002 and every 12 weeks in MOR-100, were tested for elosulfase alfa total antibodies (TAB). Positive samples were also tested for neutralizing antibodies (NAb) by detection of inhibition of elosulfase alfa binding to cation-independent mannose 6-phosphate receptor (CI-M6PR) in vitro [11]. Total immunoglobulin E (IgE) and anti-elosulfase alfa IgE were measured at baseline, as well as in the event of a serious AE (SAE) temporally related to elosulfase alfa infusion, including those requiring cessation of infusion.

### 2.6. Statistical analysis

Descriptive statistics were used to summarize outcomes at each dose level in MOR-002. Analysis of MOR-100 data was complicated by the variability in duration that each patient remained in MOR-002 before proceeding into the extension study. This variability resulted in patients entering MOR-100 with different durations of prior treatment exposure. For better understanding of outcomes relative to treatment duration, and to account for missing data in the extended study, a post hoc analysis was performed using recorded assessment dates to determine actual treatment duration in 3-month increments. A mixed-model analysis, including repeated measures for patients and months, was used to estimate least squares assessment outcomes by treatment duration.

## 3. Results

### 3.1. Patient disposition and baseline characteristics

Of the 20 individuals with Morquio A syndrome who enrolled in MOR-002, 12 were male and 8 were female aged 4–16 years of age (median age, 7.9 years) (Table 1). One four-year-old patient was 6 weeks younger than the 5-year minimum age and was granted an exemption. The patients exhibited a wide range of functional

**Table 1**  
Patient demographics in the MOR-002 and MOR-100 studies.

	MOR-002	MOR-100
	(n = 20)	(n = 17)
<b>Age at enrollment (years)</b>		
Mean $\pm$ SD	8.4 $\pm$ 2.90	8.1 $\pm$ 2.78
Median	7.9	7.5
Min, Max	4, 16	4, 16
<b>Age group, n (%)</b>		
$\geq$ 4 to < 8 years	10 (50.0)	9 (52.9)
$\geq$ 8 to < 10 years	5 (25.0)	5 (29.4)
$\geq$ 10 to < 18 years	5 (25.0)	3 (17.6)
<b>Sex, n (%)</b>		
Female	8 (40.0)	8 (47.1)
Male	12 (60.0)	9 (52.9)
<b>Baseline endurance</b>		
6MWT (mean $\pm$ SD)	266.9 $\pm$ 137.9	N/A
3MSCT (mean $\pm$ SD)	38.9 $\pm$ 25.39	N/A

3MSCT, 3-min stair climb test; 6MWT, 6-min walk test; N/A, not applicable.

impairment and organ system involvement due to the heterogeneity of the disease.

Eighteen of the 20 patients completed the dose-escalation and continuation periods. Two individuals withdrew during the 0.1 mg/kg qw portion of the dose-escalation period: 1 patient withdrew due to a type I hypersensitivity reaction and that patient's sibling withdrew from the study in the absence of AEs by request. At the principal investigator's discretion, a third participant discontinued treatment at week 45 due to recurrent infusion reactions (IR) but continued to participate in follow-up assessments at weeks 48 and 72.

All 17 patients who completed MOR-002 without discontinuing study drug enrolled in MOR-100 and remained enrolled for the duration of the trial. Thirteen of 17 (76.5%) chose to receive infusions at home and received a median of 17 infusions (range, 11–27) during MOR-100. The remaining 4 patients opted not to participate in home infusions due to personal preference or logistic considerations. No deaths occurred during either study.

### 3.2. PK and PD

PK analysis of elosulfase alfa was performed at week 24 for 1.0 mg/kg qw and week 36 for 2.0 mg/kg qw in the MOR-002 trial. PK parameters could not be determined for individuals receiving 0.1 mg/kg qw at weeks 1 and 12 because the majority of sample measurements were below the lower limit of quantification (10 ng/mL). Mean plasma concentrations of elosulfase alfa at each of the doses are shown in Fig. 1A. The mean  $t_{1/2}$  of elosulfase alfa was 44 min at 1.0 mg/kg qw and 35 min at 2.0 mg/kg qw. Increases in the mean values for  $C_{max}$  and  $AUC_{0-t}$  far exceeded the increases in dose between 0.1, 1.0, and 2.0 mg/kg qw, and this nonlinearity was reflected by corresponding decreases in  $CL$ ,  $V_{dz}$ , and  $V_{dss}$  (Table 2).

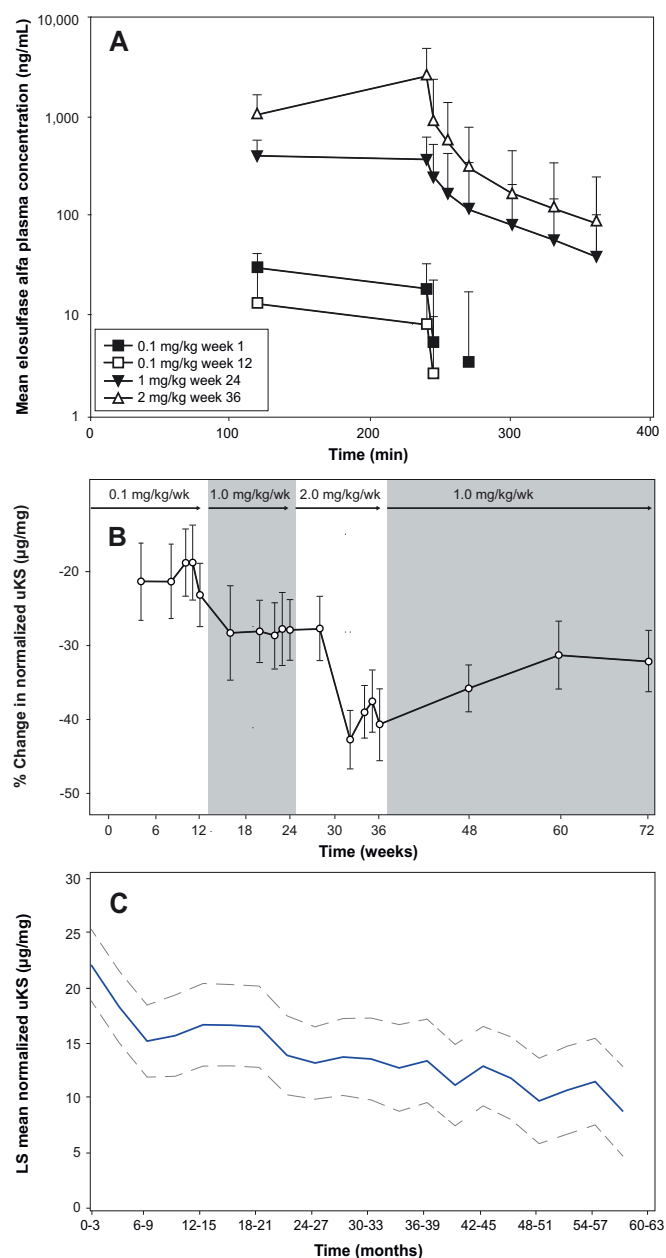
During the MOR-002 trial, normalized levels of the PD marker uKS decreased concurrently with increasing doses of elosulfase alfa (Fig. 1B). Following 12 weeks of treatment at 0.1 mg/kg qw, there was a mean  $\pm$  SD percentage reduction of 23.2%  $\pm$  19.04% in uKS levels from baseline. After an additional 12 weeks of treatment with elosulfase alfa 1.0 mg/kg qw, uKS levels were further reduced to 27.9%  $\pm$  17.92% from baseline. The greatest reduction during MOR-002 was observed at the completion of 12 weeks of treatment at the 2.0 mg/kg qw dose (40.6%  $\pm$  20.16% compared with baseline). During the continuation period of MOR-002, patients were treated at the lower dose of 1.0 mg/kg qw and by week 72, the percentage reduction from baseline had decreased to 32.2%  $\pm$  17.10%. With the return to elosulfase alfa 2.0 mg/kg qw in MOR-100, uKS levels resumed a gradual decline, which was maintained throughout the study.

The overall trend in uKS was analyzed by mixed-model analysis at 3-month intervals. Fig. 1C illustrates the declining trend in LS mean uKS over the course of MOR-002 and MOR-100.

### 3.3. Clinical outcomes

#### 3.3.1. 6-Min walk test

The mean  $\pm$  SD 6MWT distance was 266.9  $\pm$  137.39 m at baseline. After 12 weeks of elosulfase alfa 0.1 mg/kg qw treatment, mean  $\pm$  SD distance decreased to 250.8  $\pm$  130.14 m, with patients experiencing a mean  $\pm$  SD change from baseline of  $-20.7 \pm 85.95$  m. However, this trend reversed after 12 weeks of subsequent 1.0 mg/kg qw dosing, with a 16.3  $\pm$  71.74 m increase from baseline. Following 12 weeks of 2.0 mg/kg qw dosing, the mean  $\pm$  SD change from baseline remained positive at 13.8  $\pm$  63.25 m. With the reduction in dose back to the 1.0 mg/kg qw level for 12 weeks during the extension study, the mean  $\pm$  SD change from baseline was 4.0  $\pm$  87.24 m (Fig. 2A). To analyze the long-term 6MWT outcomes, a mixed-model analysis of the combined MOR-002/MOR-100 dataset was performed over 3-month intervals and showed no significant trend toward decline over 5 years, with the least squares mean distance



**Fig. 1.** Pharmacokinetics and pharmacodynamics of elosulfase alfa in patients in MOR-002 and MOR-100. (A) MOR-002. Mean plasma concentration of elosulfase alfa (ng/ml) by dose over time (min). (B) MOR-002. Percent change in normalized urine keratan sulfate (uKS;  $\mu\text{g}/\text{mg}$ ) by week. Sample size ( $n$ ) varied from 16 to 20. (C) MOR-002 and MOR-100. Least squares mean normalized urine keratan sulfate (uKS;  $\mu\text{g}/\text{mg}$ ) by month. Dashed lines represent the 95% CI. Least squares (LS) mean is based on mixed-model analysis performed with outcome modeled at 3-month intervals with repeated measures for patients and months.

remaining stable at approximately 270 m (Fig. 2B). The downward trend seen while patients were receiving the suboptimal 0.1 mg/kg qw dose and natural history data [1] both suggest that this stability would have been unlikely in the absence of treatment. The expected downward trend of 6MWT results in Morquio A is illustrated in Supplemental Fig. 1.

### 3.3.2. 3-Min stair climb test

The mean  $\pm$  SD 3MSCT rate was  $38.9 \pm 25.39$  stairs/min at baseline. Following a change from baseline of  $5.7 \pm 14.01$  stairs/min at week 6, the rate at week 12 returned to near baseline with a mean change of  $0.3 \pm 14.07$  stairs/min; subsequent MOR-002 assessments

showed continuously increasing changes from baseline up to an improvement of  $9.7 \pm 14.42$  stairs/min at week 48, and this improvement was maintained at week 72 ( $9.7 \pm 13.91$  stairs/min) (Fig. 2C). The least squares mean rate remained relatively stable over 5 years at approximately 37 stairs/min, with no trend toward decline (Fig. 2D).

### 3.3.3. Respiratory function

No dose-related trends in respiratory function emerged in MOR-002. All assessments improved relative to baseline at all time points, with the exception of a mean  $\pm$  SD decrease of  $1.8\% \pm 15.42\%$  in  $\text{FEV}_1$  at week 24. At week 72, mean  $\pm$  SD percentage increase from baseline was  $12.5\% \pm 14.88\%$ ,  $8.4\% \pm 16.22\%$ , and  $18.4\% \pm 20.77\%$  for FVC,  $\text{FEV}_1$ , and MVV, respectively. Least squares mean FVC,  $\text{FEV}_1$ , and MVV all increased gradually from baseline over 5 years (Fig. 3).

### 3.3.4. Patient-reported outcomes

At baseline, MPS-HAQ results were reflective of moderate impairment in mobility and self-care, with mean  $\pm$  SD scores of  $5.0 \pm 2.96$  and  $4.9 \pm 2.69$ , respectively (0 = not difficult at all; 10 = extremely difficult; 11 = unable to do). The mean  $\pm$  SD caregiver assistance domain score was  $31.1 \pm 7.59$  (48 = complete assistance required). Over the course of MOR-002, MPS-HAQ scores were variable with no consistent trends detected. At week 72, the self-care, mobility, and caregiver assistance domain scores were  $5.5 \pm 3.03$ ,  $4.9 \pm 2.72$ , and  $31.4 \pm 10.52$ , respectively. Over 5 years, the least squares mean self-care, mobility, and caregiver assistance domain scores declined slightly, suggestive of maintenance or possible improvement of functional abilities (Fig. 4).

## 3.4. Safety

### 3.4.1. AEs and SAEs

The safety population analysis included patients who received  $\geq 1$  dose of elosulfase alfa. Over the course of MOR-002 and MOR-100, all patients experienced  $\geq 1$  AE, with most being mild or moderate in severity (Table 3). The most common AEs determined by study investigators to be possibly or probably related to study drug were pyrexia (45.0%), headache (40.0%), and increased total IgE levels (30.0%) (Supplemental Table 1).

The majority of SAEs were consistent with complications of Morquio A syndrome [12] and difficulties with cannulation. The most common study drug-related SAEs were injection site reactions (10.0%) and pyrexia (10.0%); the majority of remaining SAEs were primarily a result of hypersensitivity reactions (addressed in detail in Section 3.4.2). The incidence of AEs and SAEs did not appear to increase in frequency with increased dose or exposure time, regardless of whether they were determined to be related or unrelated to the study drug (Supplemental Table 1).

### 3.4.2. Hypersensitivity events

Throughout MOR-002 and MOR-100, 12 patients (60.0%) experienced at least one hypersensitivity AE as identified by the broad angioedema or anaphylactic reaction SMQ (Supplemental Table 2). However, hypersensitivity AEs were only considered possibly or probably related to elosulfase alfa in 5 of these patients (25.0%). During MOR-002, 2 patients (10.0%) experienced hypersensitivity AEs identified as possibly or probably related to study drug. One patient receiving a 0.1 mg/kg qw infusion had not received antihistamine before infusion and at week 11 experienced a grade 4 type I hypersensitivity SAE requiring medical intervention that included oxygen, steroid, epinephrine, and antihistamine. This patient tested positive for drug-specific IgE and discontinued study treatment because of the SAE. Another patient experienced recurrent IR SAEs during weeks 13–15, including gastrointestinal symptoms and reduced oxygen saturation. Pre-infusion medication had been administered from weeks 15 through 45. At week 27, the patient experienced pyrexia, shivering, tachycardia, and



**Table 2**  
Pharmacokinetic parameters of elosulfase alfa by dose.

Parameter	Elosulfase alfa 0.1 mg/kg qw Week 1			Elosulfase alfa 0.1 mg/kg qw Week 12			Elosulfase alfa 1.0 mg/kg qw Week 24			Elosulfase alfa 2.0 mg/kg qw Week 36		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
AUC <sub>inf</sub> (min·ng/mL)	0	–	–	0	–	–	7	119,127	51,722	11	409,352	267,503
AUC <sub>0–t</sub> (min·ng/mL)	10	5635	2238	10	3606	840	17	89,428	42,582	16	335,814	233,133
C <sub>max</sub> (ng/mL)	17	34.3	14.7	17	25.5	7.9	17	503	208	18	2023	2056
T <sub>max</sub> (min)	17	159	72	17	137	44	17	175	69	18	196	83
t <sub>1/2</sub> (min)	0	–	–	0	–	–	7	43.7	21.8	11	35	25
CL (mL/min/kg)	0	–	–	0	–	–	7	10.2	5.6	11	7.5	5.4
V <sub>dZ</sub> (mL/kg)	0	–	–	0	–	–	7	563	265	11	281	210
V <sub>dss</sub> (mL/kg)	0	–	–	0	–	–	7	1047	875	11	643	853

AUC<sub>inf</sub>, area under the curve from time 0 to infinity; AUC<sub>0–t</sub>, area under the curve from time 0 to last measurable concentration; CL, clearance; C<sub>max</sub>, maximum observed concentration in plasma; qw, once weekly; t<sub>1/2</sub>, terminal half-life; T<sub>max</sub>, time to reach C<sub>max</sub>; V<sub>dss</sub>, volume of distribution based at steady state; V<sub>dZ</sub>, volume of distribution based on the terminal rate constant.

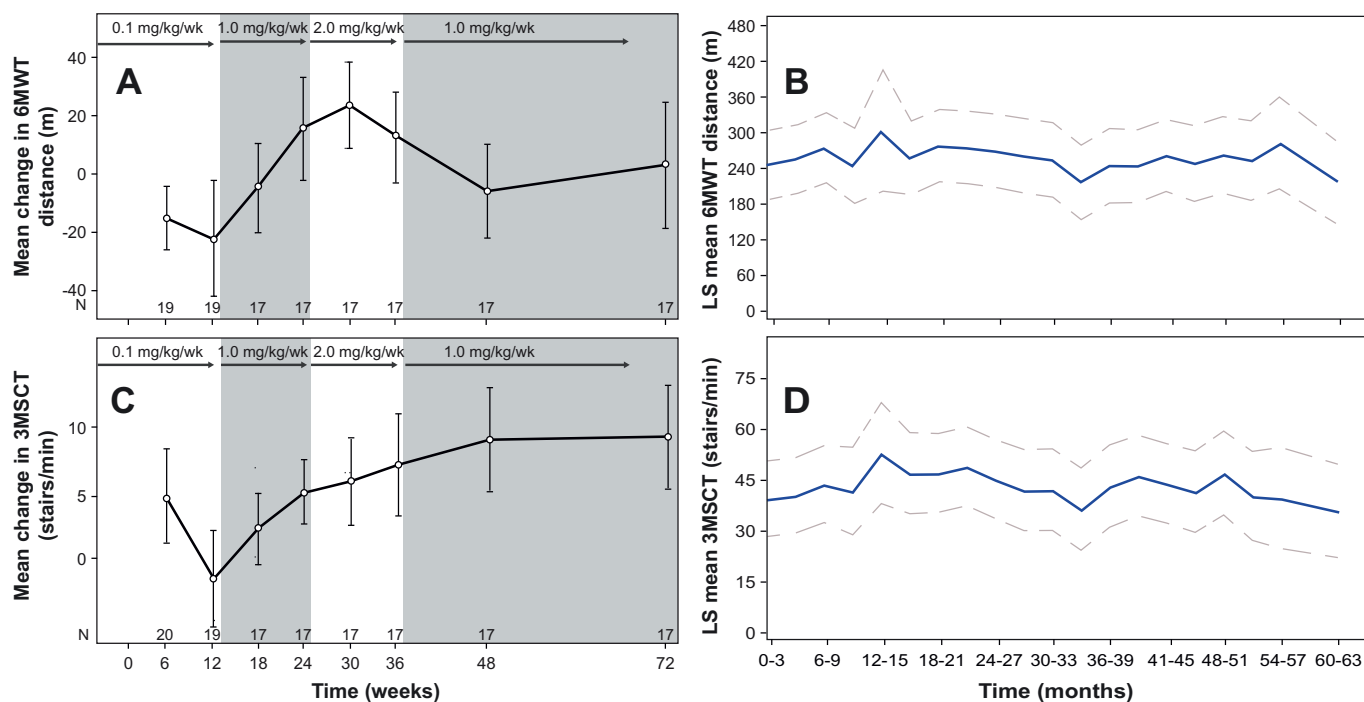
vomiting during a 2.0 mg/kg qw infusion; however, the patient continued qw infusions without AEs from weeks 28 through 35 before experiencing gastrointestinal symptoms during an infusion at week 36, which also coincided with administration of an H1N1 vaccination. Samples obtained at multiple time points during this period tested negative for drug-specific IgE. The patient continued to experience IRs, including urticaria and gastrointestinal symptoms, after reduction of the dose to 1.0 mg/kg qw and modification of the infusion rate through week 45. IV steroids were administered to address study drug-related AEs that occurred at each visit from weeks 39 through 45. Tryptase levels in conjunction with IRs were normal; however, total IgE levels were elevated at week 39. In spite of multiple strategies to tolerate the infusions, including combinations of H1/H2 blockers, leukotriene antagonists and steroids, the patient discontinued treatment at week 45 due to repeated IRs but remained in the study for follow-up assessments.

During MOR-100, hypersensitivity AEs possibly or probably related

to study drug occurred in 3 patients (17.6%) (Supplemental Table 2). One patient experienced 52 events of grade 1 or 2 urticaria that were primarily localized to the hands. This patient was successfully managed by changing the rate of infusion and was considered appropriate for home administration of the study drug by the investigator.

### 3.5. Immunogenicity

By week 18, all patients had developed elosulfase alfa-binding TAB, and these responses were sustained throughout the MOR-002 and MOR-100 trials (Supplemental Table 3 and Supplemental Fig. 2). At week 144, TAB titer was a mean ± SD of 629,877 ± 1,322,455 and a median (range) of 197,000 (2430–5,310,000). These results were similar to those reported in the larger phase 3 MOR-004 pivotal trial and its extension study MOR-005, with respective means ± SD of 167,737 ± 398,717 and 1,234,148 ± 2,618,483, and medians (range) of 65,600 (0–1,770,000) and 393,500 (810–15,900,000)



**Fig. 2.** Endurance outcomes. (A) MOR-002 6-min walk test (6MWT) mean change from baseline. (B) MOR-002/MOR-100 combined least squares (LS) mean 6MWT distance (m) by months of treatment exposure. (C) MOR-002 3-min stair climb test (3MSCT) mean change from baseline. (D) MOR-002/MOR-100 combined LS mean 3MSCT rate (stairs/min) by months of treatment exposure. Error bars represent SE. Dashed lines represent the 95% CI. LS means are based on mixed-model analysis performed with outcomes modeled at 3-month intervals with repeated measures for patients and months.

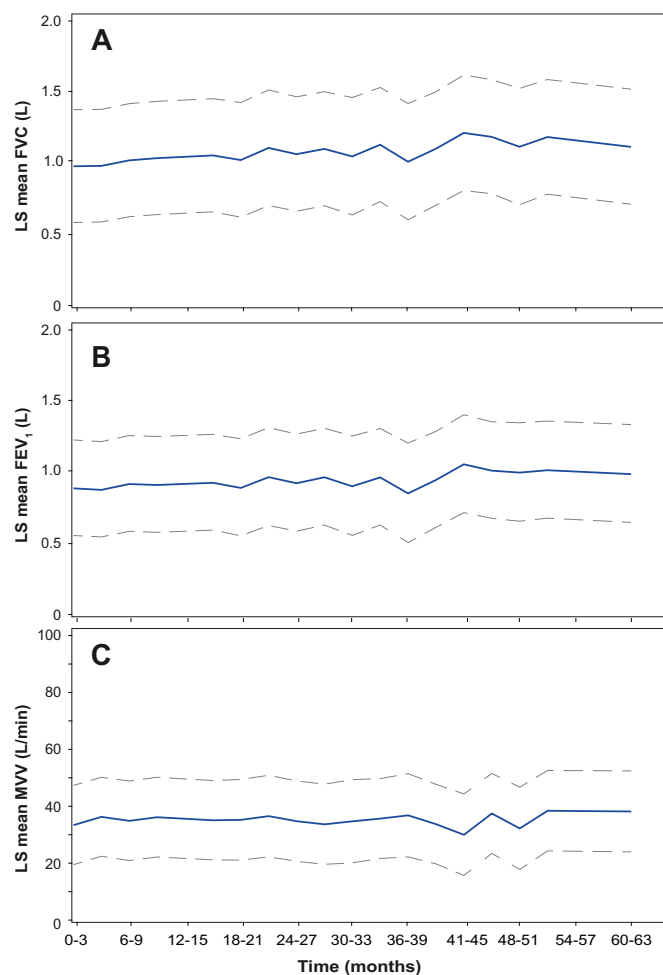


Fig. 3. Least squares (LS) mean (A) forced vital capacity (FVC), (B) forced expiratory volume in 1 s ( $FEV_1$ ), and (C) maximum voluntary ventilation (MVV) by months of treatment exposure for the MOR-002/MOR-100 combined data set. Dashed lines represent the 95% CI. LS means are based on mixed-model analysis performed with outcomes modeled at 3-month intervals with repeated measures for patients and months.

[11,13].

Four patients tested positive for elosulfase alfa-specific IgE, one from MOR-002 described above who withdrew at week 11 due to a grade 4 type I hypersensitivity reaction and three in whom elosulfase alfa IgE antibodies were transiently detected during MOR-100 (3/17 [17.7%]). One patient tested positive at baseline and week 132, the second tested positive at week 12, and the third tested positive at weeks 24 and 96 (Supplemental Table 3). Drug-specific IgE positivity was not associated with hypersensitivity AEs in these 3 patients.

The overall proportion of patients positive for NAb was 45.0% in MOR-002 and 93.8% in MOR-100. NAb-positive patients in MOR-002 were initially observed at week 6, and the positivity fluctuated throughout MOR-002 and MOR-100 (Supplemental Table 3). In MOR-002, the incidence of NAb-positive patients ranged between 17.6% (week 18) and 47.1% (week 60), peaking at 93.8% in MOR-100 (week 144). NAb responses were transient or intermittent in many cases, with 60% of patients reverting to NAb-negative status at least once.

The presence of NAb was correlated with reduced clearance and increased plasma  $t_{1/2}$  of the drug. Patients with NAb positivity at the time of PK evaluation had on average an approximately 1.5- to 3-fold increase in elosulfase alfa  $t_{1/2}$  and an approximately 2-fold decrease in CL at 1.0 and 2.0 mg/kg qw doses. This prolonged  $t_{1/2}$  and decreased CL in patients positive for NAb was mirrored by approximately a 2-fold increase in  $AUC_{inf}$  and  $C_{max}$  at weeks 24 and 36 (Table 4). Despite these PK alterations, the presence of elosulfase alfa-specific TAb or NAb

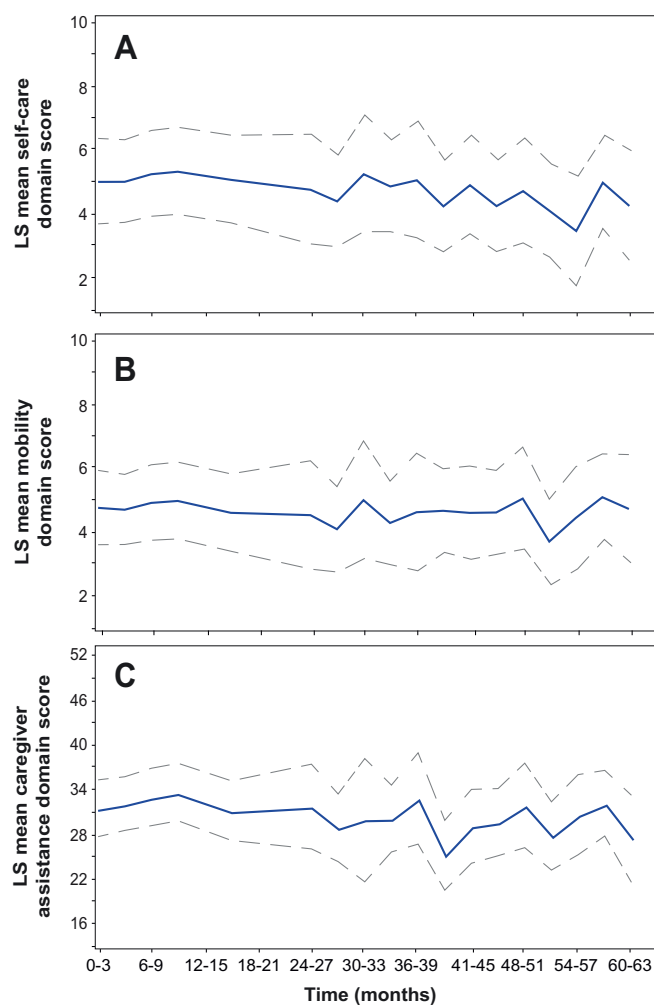


Fig. 4. Least squares (LS) mean (A) self-care, (B) mobility, and (C) caregiver assistance domain scores of the Mucopolysaccharidosis Health Assessment Questionnaire by months of treatment exposure for the MOR-002/MOR-100 combined data set. Dashed lines represent the 95% CI. LS means are based on mixed-model analysis performed with outcomes modeled at 3-month intervals with repeated measures for patients and months.

responses had no apparent relationship with change in normalized uKS levels or endurance measures in the MOR-002 or MOR-100 trials (Supplemental Fig. 3). Both the TAb titer and NAb positivity rate through week 144 were evaluated with respect to the change from baseline in uKS levels, 6MWT distance, and 3MSCT rate. Patients with higher TAb titers or NAb positivity did not have increased uKS values or decreased endurance measures. Additionally, TAb titer or NAb positivity did not appear to be related to the incidence or severity of hypersensitivity AEs (Supplemental Table 4). Patients with TAb titers greater than the study mean did not have more hypersensitivity AEs than those with TAb titers lower than the mean (Supplemental Table 5). Overall, immunogenicity findings did not identify a link to clinical outcomes or safety, similar to results reported previously for the larger phase 3 pivotal trial [11,13].

### 3.6. Home infusion

Patients in MOR-100 were given the option of receiving treatment at home rather than in a medical setting. Thirteen of 17 patients elected to receive a total of 242 infusions at home. Mean dosing compliance in patients receiving home infusions (86.1% [ $n = 13$ ]) was similar to overall MOR-100 compliance (87.0% [ $n = 17$ ]). Home infusions with elosulfase alfa were well tolerated. All 13 patients reported  $\geq 1$  AE

**Table 3**  
Overall summary of all adverse events.

n (%)	MOR-002				Continuation period 1.0 mg/kg qw (n = 18)	Overall (n = 20)	MOR-100	MOR-002/MOR-100
	0.1 mg/kg qw (n = 20)	1.0 mg/kg qw (n = 18)	2.0 mg/kg qw (n = 18)	2.0 mg/kg qw (n = 17)			Combined (n = 20)	
Patients with ≥1 reported AE	18 (90)	18 (100)	17 (94.4)	17 (94.4)	20 (100.0)	17 (100.0)	20 (100.0)	
Any study drug-related AE	12 (60.0)	10 (55.6)	7 (38.9)	8 (44.4)	14 (70.0)	16 (94.1)	19 (95.0)	
Any SAE	6 (30.0)	2 (11.1)	8 (44.4)	6 (33.3)	14 (70.0)	15 (88.2)	19 (95.0)	
Any study drug-related SAE	2 (10.0)	1 (5.6)	2 (11.1)	1 (5.6)	4 (20.0)	6 (35.3)	9 (45.0)	
Any AEs causing study discontinuation	1 (5.0)	0	0	0	1 (5.0)	0	0	
Any study drug-related AEs causing permanent study discontinuation	1 (5.0)	0	0	0	1 (5.0)	0	1 (5.0)	
Death	0	0	0	0	0	0	0	

AE, adverse event; qw, once weekly; SAE, serious adverse event.

**Table 4**  
Pharmacokinetics and neutralizing antibody response by dose of elosulfase alfa.

NAb Status	AUC <sub>inf</sub> (min-ng/ mL)	AUC <sub>0-t</sub> (min-ng/ mL)	C <sub>max</sub> (ng/ mL)	t <sub>1/2</sub> (min)	CL (mL/ min/ kg)	V <sub>d</sub> (mL/ kg)
<b>1.0 mg/kg qw, week 24</b>						
Positive (n = 4)	Mean 152,573 SD 53,045	142,037 50,455	685 169	54.0 6.4	7.0 2.0	546 171
Negative (n = 13)	Mean 94,043 SD 38,948	79,892 33,277	472 204	35.9 27.0	12.6 6.4	575 347
<b>2.0 mg/kg qw, week 36</b>						
Positive (n = 7)	Mean 572,412 SD 277,543	439,832 291,318	3296 2875	53.7 18.7	4.5 2.5	359 252
Negative (n = 11)	Mean 273,468 SD 180,958	254,912 146,383	1212 611	19.6 18.4	10.0 6.0	217 161

AUC<sub>inf</sub>, area under the curve from time 0 to infinity; AUC<sub>0-t</sub>, area under the curve from time 0 to last measurable concentration; CL, clearance; C<sub>max</sub>, maximum observed concentration in plasma; qw, once weekly; t<sub>1/2</sub>, terminal half-life; V<sub>d</sub>, volume of distribution based on the terminal rate constant.

during the home infusion period. The most common AEs occurring during home infusion were headache (54%), pain in extremity (38%), cough (31%) and arthralgia, nasopharyngitis, neck pain and vomiting (23% each). These AEs were consistent with those seen overall in MOR-100 and occurred at a lower incidence than in the overall population, in which the most common AEs were cough (94%), pyrexia, nasopharyngitis and headache (88% each), and pain in extremity and vomiting (82% each). One patient experienced a grade 4 lower respiratory tract infection SAE (not considered related to elosulfase alfa) during home infusion and 3 patients experienced hypersensitivity AEs. No patients receiving home infusions experienced drug-related AEs that led to treatment discontinuation or required medical intervention.

#### 4. Discussion

This study provides PK and PD data on the administration of elosulfase alfa to patients with Morquio A syndrome in the United Kingdom, as well as safety, immunogenicity, and clinical outcome data over a period of 5 years.

The primary objective of this study was to assess the safety and tolerability of escalating doses of elosulfase alfa. Elosulfase alfa was generally well tolerated at all of the doses explored in MOR-002, and no new safety signals were identified during sustained treatment with elosulfase alfa 2.0 mg/kg qw over the remainder of the 5 years of treatment. Although all study patients experienced AEs, the majority were mild or moderate in severity. Hypersensitivity reactions were commonly experienced and were managed with additional medication (s) and/or by altering the infusion rate. One patient experienced a type I

hypersensitivity reaction and another experienced recurrent IRs, both leading to discontinuation of the study. This 10% discontinuation rate due to hypersensitivity AEs was not observed in the subsequent phase 3 trial [6] and may reflect a more cautious approach taken in this first-in-human study.

Patients in the MOR-002 trial and the MOR-100 long-term extension generally maintained 6MWT and 3MSCT outcomes equivalent to baseline or slightly higher. However, surgical procedures were not excluded during this study, which could account for some of the gains or losses. The small sample size and absence of a control group also prevent evaluation of efficacy. Nevertheless, these results contrast those of the Morquio A Clinical Assessment Program (MorCAP) natural history study, which followed the progression of untreated Morquio A syndrome over 2 years and reported declining 6MWT distances in untreated individuals over this period [1]. It should be noted, however, that the mean age of patients at baseline in the MorCAP observational study was higher than that at the MOR-002 baseline (14.4 ± 11.97 years vs 8.4 ± 2.90 years).

Patients with Morquio A syndrome are at increased risk of declining pulmonary function as the condition progresses; however, in this study, FVC, FEV<sub>1</sub>, and MVV all increased over time. These increases may be partially attributable to growth [5], but without an age-matched group of untreated patients providing a comparison, the true impact of treatment on pulmonary function could not be fully assessed in this study. Similarly, interpreting the meaningfulness of the MPS-HAQ outcomes is challenging in these younger patients who may or may not have experienced increased self-sufficiency and decreased reliance on caregivers as part of their normal development, even in the absence of treatment. Nevertheless, quality of life measures, including mobility and self-care domains, have been shown to be negatively affected in children with Morquio A syndrome [14] and would be expected to decline as the disease progresses. The patients in this study were able to maintain a consistent level of function over the 5-year study according to the MPS-HAQ domains of self-care, mobility, and caregiver assistance.

Normalized uKS levels demonstrated a robust dose-dependent PD relationship; the greatest reduction of uKS levels was observed at the conclusion of the 2.0 mg/kg qw dosing period. Additionally, the 2.0 mg/kg qw dose yielded superior plasma availability, and interestingly, increases in PK parameters such as C<sub>max</sub> and AUC<sub>0-t</sub> were nonlinear and far exceeded dose increases from 0.1 to 1.0 to 2.0 mg/kg qw. In parallel, decreases in CL, V<sub>d</sub>, and V<sub>dss</sub> were also nonlinear, suggesting possible saturation of clearance mechanisms (protease degradation and/or CI-M6PR receptor-mediated cellular uptake).

Although this study did not include a placebo arm, and dose-dependent effects were difficult to extrapolate, the PK/PD and preliminary efficacy data suggested that elosulfase alfa 2.0 mg/kg was the most appropriate dose tested for patients with Morquio A syndrome. This dose was ultimately selected for the pivotal phase 3 MOR-004 trial

[6], and higher doses were only used in a later study [15].

Consistent with previous reports, all evaluable patients developed TAB against elosulfase alfa and tested positive throughout the duration of the study. NAb capable of interfering with drug binding to CI-M6PR were also detected in almost all patients at  $\geq 1$  time points. The presence of TAB and NAb was not associated with changes in endurance (6MWT and 3MSCT) or changes in PD effect (uKS), and no relationship between the presence of drug-specific antibodies and the emergence of AEs was identified [11]. A relationship between PK parameters and NAb positivity was apparent: patients who were positive for NAb had prolonged  $t_{1/2}$  and decreased CL of elosulfase alfa at both 1.0 and 2.0 mg/kg qw.

The impact of NAb on PK parameters is consistent with what was reported in the placebo-controlled MOR-004 study [16]. Furthermore, an alternative cell-based flow cytometry NAb assay was developed to assess and titer functionally defined NAb, and similarly, no relationships were found between efficacy outcomes and NAb positivity or titer in patient samples from the MOR-004 study [17]. These data suggest that despite the persistence of TAB and high rates of NAb formation with subsequent effects on elosulfase alfa PK, neither TAB nor NAb are correlated with the incidence of AEs, loss of efficacy, or altered PD effect.

Treatment compliance and safety were similar with home and in-hospital infusions. This finding is important because patients with Morquio A syndrome require lifelong treatment. Weekly infusions in a healthcare center require great time commitments from patients, especially when long-distance travel is required. A preliminary exploration of the experience of young patients with lysosomal storage diseases and their families showed a need for more flexibility in ERT access [18]. Like study results for other lysosomal storage diseases [19,20], our results indicate that home administration of ERT for Morquio A syndrome is a feasible option that can reduce the burden of the time-consuming and disruptive visits to the healthcare center for IV treatment.

## 5. Conclusions

Despite the presence and long-term persistence of antidrug antibodies, elosulfase alfa produced a robust, ongoing PD (uKS) response and maintained tolerability and a favorable safety profile in patients with Morquio A syndrome over 5 years. Treatment compliance and safety results were comparable between in-hospital and in-home infusions. Interestingly, based on the clinical measures used, this patient cohort did not appear to experience a progressive deterioration of endurance, pulmonary function, or functional capabilities. However, whether or not this can be attributed to elosulfase alfa treatment cannot be determined in the absence of a placebo group.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgme.2018.02.011>.

## Conflicts of interest

CH is the director of FYMCA Medical Ltd. and is a consultant and has conducted research for Actelion Pharmaceuticals, Amicus Therapeutics, BioMarin Pharmaceutical Inc., Sanofi Genzyme, and Shire.

SS has conducted research for BioMarin Pharmaceutical Inc., Shire, Ultragenyx, and Alexion, and has received unrestricted research grants, travel support, and advisory board honoraria from BioMarin Pharmaceutical Inc. and Shire.

SAJ has received consulting fees, honoraria and travel support from BioMarin Pharmaceutical Inc., Shire, Genzyme, Ultragenyx, Alexion and Orchard Therapeutics.

TG has conducted research for and has received advisory board honoraria, unrestricted research grants and travel support from BioMarin Pharmaceutical Inc.

LJ, BL, YQ, SMH, and CD are employees and stockholders of BioMarin Pharmaceutical Inc.

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