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Impact of Elosulfase Alfa in Patients with Morquio A Syndrome Who Have Limited Ambulation: An Open-Label, Phase 2 Study

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Efficacy and safety of elosulfase alfa enzyme replacement therapy (ERT) were assessed in an open-label, phase 2, multi-national study in Morquio A patients aged ≥5 years unable to walk ≥30 meters in the 6-min walk test. Patients received elosulfase alfa 2.0 mg/kg/week intravenously for 48 weeks. Efficacy measures were functional dexterity, pinch/grip strength, mobility in a modified timed 25-foot walk, pain, quality of life, respiratory function, and urine keratan sulfate (KS). Safety/tolerability was also assessed. Fifteen patients received elosulfase alfa, three patients discontinued ERT due to adverse events (two were grade 3 drug-related adverse events, the other was not drug-related), and two patients missed >20% of planned infusions; 10 completed treatment through 48 weeks and received ≥80% of planned infusions (Modified Per Protocol [MPP] population). The study population had more advanced disease than that enrolled in other trials. From baseline to week 48, MPP data showed biochemical efficacy (urine KS decreased 52.4%). The remaining efficacy results were highly variable due to challenges in test execution because of severe skeletal and joint abnormalities, small sample sizes, and clinical heterogeneity among patients. Eight patients showed improvements in one or more outcome measures; several patients indicated improvements not captured by the study assessments (e.g., increased energy, functional ability). The nature of adverse events was similar to other elosulfase alfa studies. This study illustrates the considerable challenges in objectively measuring impact of ERT in very

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disabled Morquio A patients and highlights the need to examine results on an individual basis.

Key words: mucopolysaccharidosis IV; safety; physical endurance; GALNS protein, human [supplementary concept]; enzyme replacement therapy; mobility limitation

INTRODUCTION

Morquio A syndrome or mucopolysaccharidosis (MPS) IVA is an autosomal recessive lysosomal storage disorder caused by deficiencies in the glycosaminoglycan (GAG)-degrading enzyme N-acetylgalactosamine-6-sulfatase (GALNS). Lack of GALNS activity results in progressive accumulation of keratan sulfate (KS) and chondroitin-6-sulfate in lysosomes [Morris et al., 1994]. The resulting cellular and organ dysfunction leads to an array of progressively worsening clinical manifestations. Morquio A patients typically show musculoskeletal and joint issues, including short stature, short neck, chest, spine, hip, and knee abnormalities, atlantoaxial instability, and wrist deformity and hypermobility [Harmatz et al., 2013; Hendriksz et al., 2015a]. In addition, patients frequently present with non-skeletal manifestations such as cardiorespiratory compromise, spinal cord compression and myelopathy, corneal clouding, hearing loss, hepatosplenomegaly, and dental abnormalities [Harmatz et al., 2013; Hendriksz et al., 2013, 2015a]. Musculoskeletal abnormalities, joint pain, cardiorespiratory compromise, and/or myelopathy frequently result in limited endurance and mobility [Harmatz et al., 2013]. In a study including 36 children and 27 adults with Morquio A, 44% of children and 85% of adults were using a wheelchair, illustrating the progressive nature of the disease that leads to decline in walking ability [Hendriksz et al., 2014b].

The only approved disease-specific therapy for patients with Morquio A syndrome is elosulfase alfa (VIMIZIM®, BioMarin Pharmaceutical Inc., Novato, CA) enzyme replacement therapy (ERT). The pivotal phase 3 study (MOR-004; clinicaltrials.gov #NCT01275066) included 176 Morquio A patients able to walk ≥30 and ≤325 m in the 6-min walk test (6MWT). In these patients, elosulfase alfa 2.0 mg/kg/week treatment was associated with a significant improvement in endurance in the 6MWT, a rapid and sustained reduction in urine KS levels (−40.7%), and clinically meaningful and sustained improvements in respiratory function, growth, and quality of life [Hendriksz et al., 2014a, 2015b]. The extension of this study (MOR-005; clinicaltrials.gov #NCT01415427) showed sustained improvement in the 6MWT over 120 weeks. Long-term 6MWT improvements were similar in patients with baseline 6MWT distance ≤200 and >200 m and with and without walking aids [Hendriksz et al., 2016b]. In addition, a phase 2 study (MOR-008; clinicaltrials.gov # NCT01609062) including 25 patients with Morquio A with relatively good endurance (able to walk ≥200 m at baseline in the 6MWT) suggested a positive impact of ERT on exercise capacity, muscle strength, and pain [Burton et al., 2015]. Here we present the results of MOR-006 (clinicaltrials.gov #NCT01697319), a phase 2 study designed to assess the efficacy and safety of elosulfase alfa in more severely affected Morquio A patients, as defined by limited ambulation (unable to walk ≥30 m in the 6MWT).

MATERIALS AND METHODS

Study Design and Patient Selection

MOR-006 was a phase 2, open-label, multi-national study. Criteria for enrollment included confirmed diagnosis of Morquio A syndrome, age ≥5 years, and inability to walk ≥30 m in the 6MWT at the screening visit. Patients received weekly intravenous (IV) infusions of 2.0 mg/kg elosulfase alfa for 48 consecutive weeks and were then given the option to participate in an extension phase of the study for up to 96 weeks. All patients were pretreated with an appropriate dose of (non-sedating) antihistamine medication approximately 30 min to 1 hr prior to infusion to avoid hypersensitivity reactions associated with the administration of elosulfase alfa. Antipyretic medications could also be given at the discretion of the investigator. For patients with a history of reactions temporally related to drug infusion or other risk factors (e.g., history of allergies, infection, recent immunization), a sedating antihistamine could be administered, and premedication with additional agents such as H2 blockers, montelukast sodium, or steroids could be considered.

The research was prospectively reviewed and approved by a duly constituted ethics committee.

Efficacy Evaluation

Primary efficacy measures. Supplementary file 1 provides a schedule of the efficacy assessments performed during the study. Efficacy results are not presented beyond the initial 48 week treatment phase of the study as not all patients continued with assessments in the extension phase. Primary efficacy measures, assessed at baseline and then every 12 weeks, were upper extremity function, mobility, pain, and self-care and functional abilities.

Upper extremity function was assessed using the functional dexterity test (FDT) and grip/pinch tests. The FDT is a validated and timed dexterity test that assesses the ability to use the hand in daily tasks [Aaron and Jansen, 2003; Lee-Valkov et al., 2003]. Patients were allowed to stabilize the wrist by resting the forearm on the table during the test.

A grip-strength dynamometer was used to measure grip strength. One set of measurements was performed with the subject resting the elbow and forearm on the table, and a second set was obtained with the wrist unsupported, if feasible. According to the protocol, patients had to be seated in appropriately sized chairs that allowed their feet to be flat on the floor. The upper extremity to be tested needed to be positioned so that the shoulder was abducted and neutrally rotated, the elbow was flexed at 90°, the forearm was in a neutral position, and the wrist was 0–30° in extension. Three measurements were obtained for each hand, with a 20-sec rest between each trial.

A pinch meter was used to measure pinch strength. Each patient was tested with the elbow at 90°, the forearm neutral, and the wrist in neutral deviation. One set of measurements (three trials) was performed with the patient resting the elbow and forearm on the

table, and a second set was obtained with the wrist unsupported, if feasible.

Basic mobility was assessed in a modified version of the timed 25-foot walk (T25FW), which was originally developed for patients with multiple sclerosis [Polman and Rudick, 2010]. Patients could use assistive devices when doing this task. Unlike in the original test, they could "walk" on their knees, crawl, or roll, if this was their usual method of ambulation. The score for the T25FW was the average of the two completed attempts.

Pain was assessed using the Brief Pain Inventory short form (BPI-SF) in adult patients (≥18 years) and the Adolescent Pediatric Pain Tool (APPT) in children (<18 years). The BPI-SF provides information on pain intensity, as well as the degree to which pain interferes with function [http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf]. The APPT is a validated, multi-dimensional pain assessment tool for children and adolescents, which measures the location, quality, and intensity of pain [Jacob et al., 2014].

Quality of life was assessed using the Pediatric Outcomes Data Collection Instrument (PODCI) in children (<18 years) [Daltroy et al., 1998] and the short form-36 (SF-36) version 2 health survey in adults (≥18 years) (www.sf-36.org/tools/sf36.shtml). The PODCI assesses the overall health, pain, and ability to participate in normal daily activities, as well as in more vigorous activities associated with young people and has previously shown measurable improvements during ERT in patients with MPS II [White et al., 2010]. The scale scores were normalized such that a normal individual will have a score of 50 and standard deviation (SD) of 10 and lower scores indicated higher levels of disability (normative scale scoring: http://www.aaos.org/CustomTemplates/Content.aspx?id=22831&ssopc=1#pedsref). The SF-36 is a validated 36-item questionnaire that assesses eight sub-items in two sub-domains, that is, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) (www.sf-36.org/tools/sf36.shtml) [Miller et al., 2010]. Each scale as well as the two summary scores range from 0 to 100, with higher scores indicating better quality of life and a score of 50 (SD 10) being representative of the general population.

Secondary and tertiary efficacy measures. Supplementary file 1 shows the schedule of assessments of secondary and tertiary efficacy measures. Secondary efficacy measures were respiratory function and urine KS levels (normalized to creatinine). Tertiary efficacy measures included the 6MWT, anthropometric measurements (growth), and a patient impression questionnaire (PIQ). In addition, radiographs of the lumbar spine, lower extremities, and hand/wrist and DXA scans (bone density) of the lumbar spine were performed for some patients at the discretion of the investigator and/or study site. At each visit, patients were also asked about the number of times they had taken analgesic medications for Morquio A disease in the past week.

Safety Evaluation

Safety was assessed throughout the initial 48-week study period and during the extension phase by evaluating clinical laboratory tests, physical examinations, immunogenicity testing, echocardiograms, electrocardiograms, and magnetic resonance imaging scans of the cervical spine. Adverse events (AEs) and changes in concomitant medication were also recorded throughout the study. Vital signs were measured on infusion days. Serum samples were collected for immunogenicity testing prior to dose administration at baseline and at weeks 2, 4, 6, 12, 24, 36, 48, 72, and 96.

Statistical Methods

As several patients from the ITT population were not compliant with the protocol or did not remain in the study for 48 weeks due to logistical issues, acute disease related to Morquio A, or adverse reactions to the study drug, descriptive statistics of efficacy measured from baseline through week 48 are presented for a Modified Per Protocol (MPP) population. The protocol originally excluded patients who missed six or more infusions from baseline through 48 weeks. Given the small sample size, criteria were adjusted to ≥20% missed infusions, establishing the MPP population.

For the purpose of creating individual patient spider plots, variables (FDT, T25FW, quality of life [PODCI or SF-36 PCS], pain [APPT or BPI-SF], forced vital capacity [FVC], and maximum voluntary ventilation [MVV]) were converted to a 0–100 scale with 0 being the worst possible result and 100 being the best possible result (See Supplementary file 2 for more details). For each patient, efficacy variables are only shown if measured at both baseline and week 48.

Safety results are presented for up to 96 weeks for the Modified Intent-To-Treat (MITT) population consisting of all patients who were randomized to study treatment and received at least one dose of study drug.

RESULTS

Patient Characteristics

Of the 16 patients enrolled in MOR-006, 15 received at least one dose of study drug. The patient who did not receive any study treatment could not physically commit to the necessary weekly travel. Of the 15 patients treated (MITT population), 12 completed at least 48 weeks of study treatment. Two patients discontinued ERT at 4 weeks due to grade 3 drug-related AEs (infusion related reaction and hypersensitivity). One patient discontinued ERT at 21 weeks due to recurrent urinary tract infections not related to the study drug. The MITT population included six female and nine male patients; median age at enrollment was 18.7 years (range 9.8–42.4). Of the 12 patients completing 48 weeks of study treatment, two missed more than 20% of their scheduled infusions. Thus, the MPP population consisted of ten patients. Details of each of these 10 cases are included in Supplementary file 3. MPP population demographics and baseline characteristics are shown in Table I. All patients of the MPP population had very short stature (90–110 cm) and severe skeletal and joint abnormalities and most had restrictive and/or obstructive lung disease. All patients had a history of multiple surgeries, including adenoidectomy/tonsillectomy, spinal cord decompression/fusion surgery, hip or knee surgery, or tracheotomy. Only three patients were able to walk on their feet at baseline, one of them with a walking device. One patient (patient 8) had an inclusion/exclusion

TABLE I. Demographics and Baseline Characteristics of Patients Included in the Modified Per Protocol (MPP) Population

Patient	Age years at baseline	Sex	Age at Morquio A diagnosis years	Length[a] cm	Weight kg	FDT pegs/min	Method of ambulation in T25FW	T25FW speed feet/min
1	12.8	M	2.9	91	22.6	4.5	Crawling	6.9
2	18.9	M	2.3	NA	36.7	18.5	Knee walking	66.7
3	17.3	F	1.4	99	28.6	16.3	Crawling using arms only	0.6
4	29.6	M	4.3	110	32.9	11.4	Physically unable	NA
5	12.6	F	4.6	107	35.6	31.0	Physically unable	NA
6	9.8	M	2.7	106	22.2	4.0	Physically unable	NA
7	13.9	F	2.8	94	18.7	Physically unable	Physically unable	NA
8	42.2	M	42.4	90	21.2	31.0	Unassisted walking	88.2
9	31.0	M	3.9	103	37.5	13.5	Unassisted walking	21.4
10	24.5	F	3.0	97	22.3	24.0	Walker/walking frame	44.8
Mean (SE)	21.3 (3.3)			99.6 (2.4)	27.8 (2.3)	17.1 (3.4)		38.1 (14.2)

FDT, functional dexterity test; T25FW, timed 25-foot walk; NA, not availabl.
[a]Length was measured as height was difficult to obtain for most patients.

waiver granted, as he walked slightly more than 30 m (31.7 m) on the 6MWT at baseline.

Efficacy Results

Upper extremity function. The method used for the FDT was customized for some patients based on their specific physical disability (e.g., hypermobile, floppy wrists), as shown in a video of patient 3 performing the test (Supplementary file 4). However, the test was performed with similar methodology for any given patient at all time points. In the MPP population, mean FDT speed showed a trend toward improvement over 48 weeks, mainly in the dominant hand (Fig. 1A). The mean (SE) number of pegs/min for the dominant hand was 15.4 (3.5) at baseline (=0.26 pegs/sec). Mean (SE) change from baseline to week 48 was 1.4 (3.1) pegs/min. However, the improvement in FDT speed was largely caused by one patient (patient 8) with an improvement of 22 pegs/min (Fig. 1B). Of the nine patients who were able to perform the FDT at baseline, four (patients 2, 5, 8, and 9) showed an improvement in FDT speed over 48 weeks of $\geq$1 peg/min, two patients (patients 4 and 6) were stable, and two showed a decrease of $\geq$1 peg/min (patients 3 and 10) (Fig. 2). Patient 1 was unable to perform the test from week 36 onwards due to acute Morquio A disease-related complications (spinal cord compression, see Supplementary file 3).

Upper extremity function was also assessed by grip and pinch strength tests. Unfortunately, most patients had difficulty performing these test according to the study protocol, due to weak grip, very hypermobile wrists and/or short stature (i.e., 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 (data not shown).

Basic mobility. Mean (SE) speed in the T25FW at baseline was 22.9 (10.3) feet/min for the MPP population. In several cases, the T25FW was not performed either at the discretion of the investigator and/or for patients with significant pain. Six out of 10 patients in the MPP population performed the T25FW at baseline and at later visits, using different ambulation methods: three patients walked (one with the assistance of a walking device), one walked on his knees (Supplementary file 5A), one crawled, and one used her arms only (Supplementary file 5B). Patients were required to use a consistent ambulation method throughout the study. Of the six patients who performed the T25FW at baseline and later visits, three (patients 2, 3, and 10) showed $\geq$10% improvement in speed over 48 weeks (Fig. 3A), one (patient 8) showed a smaller improvement (+6.2%), one (patient 1) was unable to do the test from week 36 onwards due to acute disease-related complications, and one (patient 9) declined to do the test at 48 weeks as previous tests caused too much pain afterwards.

Only four patients performed the T25FW at week 48; mean (SE) change from baseline was 6.2 (3.6) feet/min. Although, the change from baseline appeared small, it represents a mean (SE) improvement of 75 (47) % for the four patients performing the test at both baseline and week 48 (Fig. 3B). Due to the extremely limited mobility at baseline, small improvements in T25FW speed represented great percent increases in some of the patients.

Only three patients from the MPP population (patients 2, 8, and 9) were physically able to perform the 6MWT at baseline. Only patient 8 performed the 6MWT at baseline and week 48, showing an increase from 31.7 m to 66.5 m.

Respiratory function. Results showed poor respiratory function in all patients from the MPP population as compared to patients from a Morquio A natural history study (MorCAP, N = 325) [Harmatz et al., 2013]. At baseline, mean (SE) FVC was 0.66 (0.06) L (N = 8) (vs. 1.1 L in patients $\leq$18 years and 1.5 L in patients >18 years from MorCAP), mean (SE) forced expiratory volume in 1 sec (FEV_1) was 0.49 (0.02) L (N = 8), and mean (SE) MVV was 15.35 (1.3) L/min (N = 9) (vs. 32.4 L/min in

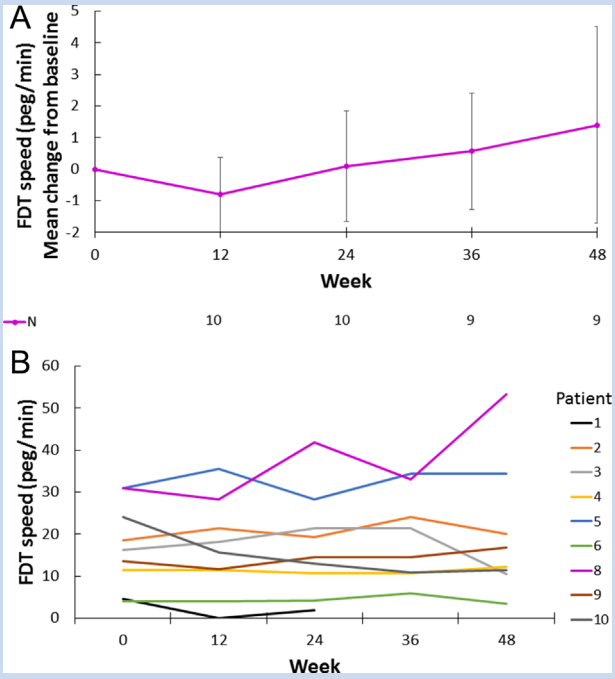

FIG. 1. Functional dexterity test (FDT) results. (A) Mean change from baseline in FDT speed (dominant hand) over time in the Modified Per Protocol (MPP) population (N = 10). Error bars represent standard errors. (B) Individual patient FDT speed over time.

FIG. 2. Summary table: outcome of efficacy assessments at week 48 versus baseline (MPP population). Green, improved; blue, stable; red, worsening; blank, test not performed or no data available at baseline and/or week 48. Footnotes: [a]FDT improvement, increase ≥1 pegs/min; stable, change <1 pegs/min; worsening, decrease ≥1 pegs/min. [b]T25FW improvement, increase speed of ≥10%; stable, change speed <10%; worsening, decrease speed ≥10%. [c]APPT pain intensity (Word Graphic Rating Scale) improvement, decrease ≥1 point; stable, change <1 point; worsening, increase ≥1 point. [d]BPI-SF pain intensity improvement, decrease ≥1 point; stable, change <1 point; worsening, increase ≥1 point. [e]PODCI improvement, increase ≥10 points; stable, change <10 points; worsening, decrease ≥10 points. [f]SF-36 PCS improvement, increase ≥10 points; stable, change <10 points; worsening, decrease ≥10 points. [g]PIQ Breathing improvement, at least a little better; stable, no change; worsening, at least a little worse. *T25FW, patient did not perform the test at 48 weeks because of pain after previous tests.

patients ≤18 years and 42.1 L/min in patients >18 years from MorCAP) in the MPP population. Overall, FVC and FEV_1 remained relatively stable and MVV increased slightly over 48 weeks (Table II). Mean percent change in MVV was +17.2% whereas FVC decreased slightly (mean change −5.4%).

At an individual patient level, changes in FVC and FEV_1 over time varied considerably among patients; MVV improved over 48 weeks in all patients assessed, with five patients (patients 3, 4, 6, 9, and 10) showing an improvement of more than 10%. One patient (patient 5) was physically unable to perform any of the respiratory function tests throughout the study. Patient 9 was physically unable to complete respiratory function tests, except MVV, at baseline and week 24, but was able to perform all tests at week 48.

Patient-reported outcomes. In the MPP population, five of ten patients reported virtually no pain (score ≤2 on the pain intensity/severity scale) at baseline in the APPT or BPI-SF. Two children (patients 3 and 5) reported pain intensity scores of 5.3 and 5.5, corresponding to medium pain [Jacob et al., 2014]. Three adult patients (patients 4, 8, and 9) had pain intensity scores ranging from three to seven and reported considerable pain interference with walking ability (pain interference scores 5–10). Unfortunately, small sample sizes (due to the use of different tools in children and adults) and high variability among patients precluded meaningful collective analysis of data. Individual patient data showed a reduction in pain intensity/severity (>1 point) over 48 weeks in two of the five patients with pain at baseline (score >3 on the pain intensity/severity scale; patients 3 and 8) (Fig. 2). Patient 3 also stopped using non-steroidal topical analgesics during the study. However, pain became more severe in two out of ten patients (patients 7 and 9).

Quality of life scores at baseline were poor as compared to healthy individuals. In children, baseline mean normalized self-reported (N = 3) and parent-reported (N = 4) PODCI scores were −41.33 (SE 11.5) and −39.25 (SE 8.2), respectively, versus an average score of 50 in healthy individuals. In adults, baseline mean SF-36 PCS was 17.3 (SE 4.5; N = 3), with 50 being the average score in healthy individuals and 0 being the lowest score possible. Mean SF-36 MCS was 57.7 (SE 5.0), similar to unaffected individuals. Similar to the pain results, small sample sizes due to different tools used in adults and children and great

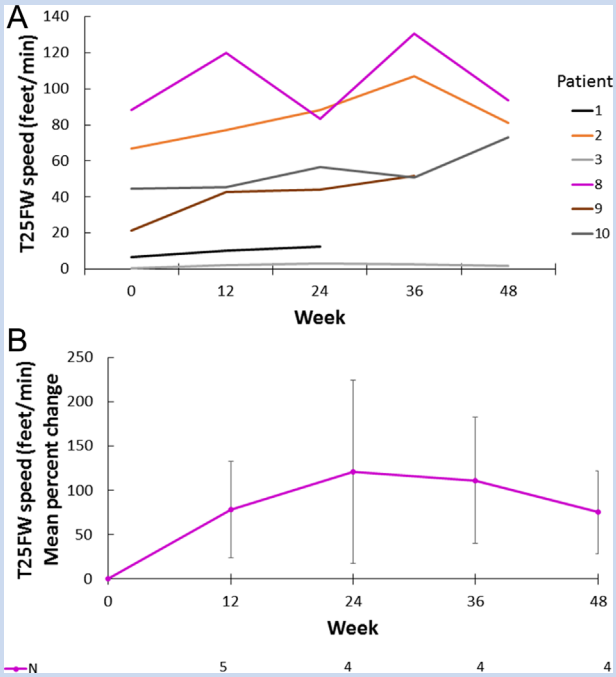

FIG. 3. Timed 25-foot walk (T25FW) results. (A) Individual patient T25FW speed over time. (B) Mean percent change from baseline in T25FWT speed over time in the Modified Per Protocol (MPP) population (N = 10). Error bars represent standard errors.

variability among patients precluded meaningful evaluation of mean changes in quality of life over 48 weeks. Individual patient data showed stable quality of life scores in most patients (Fig. 2). Patient 1 showed a considerable decrease (worsening) in the parent-reported PODCI scale, most likely due to the acute disease-related complications (spinal cord compression) he experienced during the study.

On the PIQ, six of nine patients assessed (66.7%) reported breathing ability had improved at least a little at week 48 compared to baseline (patients 4 and 5 a little better, patient 7 much better, and patients 1, 2, and 8 very much better); three patients (patients 3, 6, and 9) reported no change in breathing ability. Patient 10 did not perform the assessment at week 48.

Several patients showed improvements not captured by the study assessments. Patient 3 reported increased ability to independently perform activities such as computer typing, drinking, reaching behind her head, and drinking from a cup. Patient 8 reported increased muscle strength and dramatic improvements in sleep, breathing, and energy level. Patient 9 showed clear improvements in energy level, speech, and breathing; this patient was not able to lie flat on his back due to breathing problems at baseline, but this improved during the study. Patient 10 showed improved functional ability (she was able to comb her hair which she had been previously unable to do for many years) and improved speech (clearer voice and more understandable outside close family members).

Urine KS. Treatment with elosulfase alfa led to a rapid and sustained decrease in urine KS. At week 48, urine KS normalized for creatinine had decreased by a mean (SE) of 52.4 (3.8) % in the MPP population (Fig. 4).

Other efficacy outcomes. No conclusions can be made regarding changes in anthropometric measurements, and radiographic and DXA scans due to incomplete data collection and/or relatively short follow-up time.

Overview of individual efficacy outcomes. Figure 2 gives an overview of outcomes of efficacy measures at week 48 versus baseline in the MPP population. All patients remained stable or improved in multiple outcomes. Half of the patients did not show worsening in any of the outcomes. Improvements in patient-reported breathing ability (PIQ), FDT, and T25FW occurred most frequently.

Safety and Tolerability

The mean (SE) and range of total duration of elosulfase alfa exposure in the MITT population (N = 15) were 62.1 (8.01) and 5–96 weeks, respectively. Mean number of drug infusions was 55. Thirteen patients (86.7%) missed at least one infusion and a total of 119 (12.7%) planned infusions were missed.

Table III summarizes AEs in the MITT population. The most frequently reported drug-related AEs were headache (40.0% of patients), nausea, pyrexia, and vomiting (20.0% each). Six patients (40%) had grade 3 AEs, but most drug-related AEs were mild or moderate (CTCAE grade 1 or 2) in severity. Serious adverse events (SAEs) occurred in 47% of patients; four study drug-related SAEs were reported in two (13.3%) patients. Two patients experienced AEs (grade 3 infusion-related reaction and grade 3 hypersensitivity) that led to permanent discontinuation of the study drug. Of a total of 819 infusions, 14 (1.7%) were interrupted (11% or 1.3%) or discontinued (3% or 3.7%) due to

TABLE II. Respiratory Function Test Outcomes in Modified Per Protocol (MPP) Population

Parameter	Baseline mean (SE), N	Week 48 mean (SE), N	Week 48 mean change (SE), N	Week 48 mean % change (SE), N
FVC (L)	0.66 (0.06), N = 8	0.56 (0.05), N = 9	−0.07 (0.08), N = 8	−5.4 (11.0), N = 8
FEV_1 (L)	0.49 (0.02), N = 8	0.48 (0.04), N = 9	0.01 (0.03), N = 8	1.4 (5.8), N = 8
MVV (L/min)	15.35 (1.3), N = 9	17.94 (1.5), N = 9	2.59 (0.67), N = 9	17.2 (4.5), N = 9

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; MVV, maximum voluntary ventilation; SE, standard error of the mean.

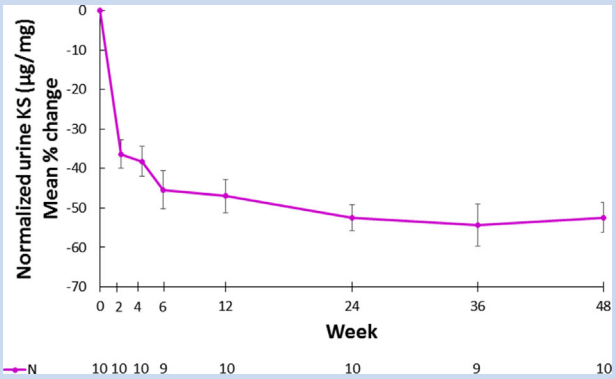

FIG. 4. Normalized urine keratan sulfate (KS) (µg/mg creatinine). Mean percent change from baseline in the Modified Per Protocol (MPP) population (N = 10). Error bars represent standard errors.

an AE requiring medical intervention (IV steroids or antihistamines).

All treated patients tested positive for anti-elosulfase alfa total antibodies (TAb) by week 4 and remained positive for the duration of the study. Neutralizing antibodies (NAb) developed in all treated patients during the study and remained positive in ten patients (66.7%) at week 48. No association was seen between TAb titer or NAb positivity rate and percent change in urine KS from baseline at weeks 24 and 48. There was also no relationship between TAb titers and the occurrence of anaphylactic reactions or study drug discontinuation. All subjects tested negative for drug-specific IgE.

TABLE III. Safety Results

	Elosulfase alfa 2.0 mg/kg/week, N = 15
Any AE, N (%)	15 (100%)
Grade 1	1 (6.7%)
Grade 2	8 (53.3%)
Grade 3	6 (40.0%)
Any study drug-related AE, N (%)	13 (86.7%)
Grade 1	5 (33.3%)
Grade 2	6 (40.0%)
Grade 3	2 (13.3%)
Any study drug-related SAE, N (%)	2 (13.3%)
Grade 3	2 (13.3%)
Any AE leading to permanent study drug discontinuation, N (%)	2 (13.3%)
Death, N (%)	0 (0.0%)
Number (%) infusions interrupted due to an AE requiring medical intervention	11 (1.3%)
Number (%) infusions discontinued due to an AE requiring medical intervention	3 (0.4%)

N, number of patients; EA, adverse event; SAE, serious adverse event.

DISCUSSION

ERT with elosulfase alfa is currently the only approved therapy that directly targets the underlying cause of Morquio A syndrome. Before its introduction, management of Morquio A patients was limited to symptom management and palliative care. Clinical trials have demonstrated that elosulfase alfa has a positive efficacy-safety profile [Hendriksz et al., 2014a; Burton et al., 2015]. However, these trials included only patients able to walk at least 30 m in the 6MWT. MOR-006 is the first study to assess the efficacy and safety of elosulfase alfa ERT in patients with limited ambulation, representing the group with severe and fixed burden of disease.

As could be expected, the patients in this study were on average older and more severely affected than the patients in other elosulfase alfa studies (Supplementary file 3) [Hendriksz et al., 2014a; Burton et al., 2015]. Only six of the ten patients included in the efficacy analysis (MPP population) were able to ambulate, either by walking (three patients, including one with the assistance of a walker) or by using other ambulation methods such as knee walking or crawling (Supplementary files 3 and 5). All patients showed poor dexterity in the FDT compared with a healthy population (Supplementary file 4); one patient from the MPP population was unable to perform the FDT. The mean baseline dexterity speed of 0.26 pegs/sec was below that reported for 3-year-old healthy children (0.41 pegs/sec) [Gogola et al., 2013]. Patients also showed more compromised respiratory function as compared to patients included in MorCAP, which likely relates to their shorter stature [Harmatz et al., 2013]. Although, all patients had severe disabilities, half of them reported no pain at baseline, most likely due to inactive lifestyle. Previous research showed that pain is an important feature of Morquio A, but that wheelchair-bound Morquio A patients experience less pain than more mobile patients [Hendriksz et al., 2014b]. The same study also showed that less mobile patients have worse quality of life. The very poor quality of life scores in the MOR-006 population seem to confirm these findings. The mean SF-36 PCS in adult patients from MOR-006 (17.3) was much lower than that recently reported for 20 adult Morquio A patients (36.5) [Ali and Cagle, 2015].

Evaluating the efficacy of ERT in this very disabled patient population proved to be challenging. Several of the severe manifestations, particularly skeletal abnormalities, were not expected to improve with ERT. Another important issue was that the 6MWT, the primary efficacy measure in the pivotal phase 3 study, was not a feasible assessment in MOR-006 as most patients were unable to walk. Therefore, endpoints used in the study were exploratory in nature, which led to difficulties evaluating the efficacy of treatment. Upper extremity function, basic mobility in the T25FW, pain, and quality of life questionnaires were used as primary efficacy measures. Upper extremity function tests were difficult to perform according to the testing protocol because of the patients' short stature and/or weak grip due to wrist deformity and hypermobility. Results of the upper extremity function tests (FDT and pinch/grip tests) and the T25FW were not comparable among individuals due to variability in test execution because of severe disease limitations. In addition,

different sites interpreted the T25FW differently: in some of the centers, patients who were unable to walk were allowed to use different ambulation methods, such as crawling or knee walking, while other sites did not perform the test in patients unable to walk on their feet. It should be noted that the original T25FW, developed for use in patients with multiple sclerosis, does not allow any ambulation methods other than walking [Polman and Rudick, 2010]. The interpretation of the pain and quality of life questionnaire results was hampered by great variability in outcomes between and within patients and small sample sizes, as different tests were used for children and adults. Psychological, social, and logistical issues also influenced treatment outcomes in some cases. For some patients, the burden of traveling long distances for infusions and assessments might have limited the beneficial effects of ERT. One of the patients was very demotivated by fear of losing funding and care support if his condition should improve.

Because of the great clinical heterogeneity between the patients included in this study, treatment goals differed from patient to patient. In addition, problems with test execution depended on the unique physical limitations of each patient. Therefore, there was not a single measure that was able to capture meaningful changes in all patients, underlining the need to evaluate the impact of treatment on an individual basis in severely disabled Morquio A patients. Deciding which tests should be used in a specific patient to evaluate treatment impact is challenging and should be based on several criteria, including the type and severity (in terms of the impact on the patient's daily living) of clinical manifestations, the potential for improvement in these clinical manifestations, the capability of the patient to perform the test, and the patient's expectations of treatment.

Despite the severe physical limitations of the patients and problems with test execution and interpretation, improvements from baseline were seen in several outcome measures after 48 weeks of ERT in most patients. Mean dexterity speed increased in half of the patients tested and remained stable in 25%. Notably, most of these patients were adults, whereas in a healthy population average dexterity speed declines after the age of 17 years [Aaron and Jansen, 2003]. In addition, most patients who were able to perform the T25FW at baseline showed increased speed over time. Factors that may have improved performance in this test (e.g., pain, fatigue, muscle strength, respiratory function) differ from patient to patient. However, as patients used their usual method of ambulation (walking, crawling, knee walking), any improvement is expected to facilitate their ability to perform activities of daily living. In addition, patient-reported impression of breathing ability (PIQ) improved in most cases. Although, all patients showed small improvements in MVV, no meaningful improvements in FVC and FEV_1 were seen over 48 weeks. The difference between MVV and spirometry results may be due to the fact that the MVV test is easier to perform than spirometery in a severely limited population and may be influenced more by changes in neuromuscular function. Longer follow-up time may be necessary to identify positive effects of treatment on respiratory function. Long-term (120-week) follow-up data from the extension of the elosulfase alfa phase 3 study (MOR-005) showed early improvements in MVV followed by improvements in FEV_1 and FVC which developed over the course of the extension study [Hendriksz et al., 2014a, 2016a]. Importantly, several patients reported subjective improvements that were not captured by the study assessments, such as increased energy and better ability to type, lift and drink from a cup, comb hair, or stand up without braces. Some of these improvements were reported to greatly impact the patient's daily life, but these improvements are not captured by current quality of life tools. Of the ten patients in the MPP population, only one discontinued ERT after the study. Nine patients continued on therapy, which means that they have gained enough benefit to endure a once weekly infusion lasting about 7 hr from set-up to end.

The dose of elosulfase alfa of 2.0 mg/kg/week used in this study is the recommended dose as established in a previous dose-escalation study and the pivotal phase 3 study (MOR-004) [Hendriksz et al., 2012, 2014a]. As the pivotal study excluded Morquio A patients with limited ambulation, it is uncertain whether this is also the optimal dosing regimen for patients with more advanced disease; future study is warranted.

The safety analysis of MOR-006 showed that the nature of AEs was generally consistent with other studies in Morquio A patients [Hendriksz et al., 2014a; Burton et al., 2015]. However, severity and impact of AEs were somewhat greater, as was to be expected with this sicker patient population (a larger percent of grade 3 AEs and SAEs overall and more AE-associated discontinuations). Overall, 1.7% of infusions were interrupted or discontinued due to an AE in MOR-006 versus 1.3% in the phase 3 MOR-004 study [Hendriksz et al., 2014a]. Antibody development was universal, similar to previous studies [Hendriksz et al., 2014a; Burton et al., 2015]. This initial antibody development had no apparent impact on the efficacy or safety of ERT. The impact of persistent and increasing antibody titers needs to be studied in the long-term.

CONCLUSIONS

The MOR-006 study demonstrates that ERT with elosulfase alfa has an acceptable safety profile, even in severely disabled Morquio A patients who may not tolerate even mild infusion related reactions, and suggests the potential for beneficial effects in these patients. Most patients experienced improvement in at least one of the domains assessed. However, lack of validated tools, issues with test execution, small sample sizes, irreversibility of some symptoms, and clinical heterogeneity among patients hampered interpretability of outcomes across the study. In addition, important patient-reported improvements in ability to carry out activities of daily living were not captured well by study assessments. As traditional tools were developed for mean populations and not for the extremes, the challenge will be to develop tools and measures that could capture the patient-reported benefits in this severely affected patient population. The outcomes of this study also stress the need to examine the impact of elosulfase alfa on an individual basis in severely disabled Morquio A patients. Regardless of which assessments are determined to be the most feasible and appropriate for a particular patient, collection of pre-treatment data and consistent assessment execution methodology are essential for capturing the effects of ERT.

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CONFLICTS OF INTEREST

Dr. Paul R. Harmatz, Dr. Eugen Mengel, Dr. Barbara K. Burton, Dr. Christian J. Hendriksz, Dr. Tarekegn Geberhiwot, Dr. Nicole Muschol, and Dr. Elisabeth Jameson were primary investigators of the study, sponsored by BioMarin Pharmaceutical Inc. Dr. Andrea Jester, Dr. Kenneth I. Berger, and Dr. Marsha Treadwell were consultants to the study. Zlatko Sisic and Celeste Decker are employees of BioMarin. Dr. Harmatz reports grants, personal fees, and non-financial support from BioMarin, during the conduct of the study; Dr. Harmatz also received personal fees, and non-financial support from Shire, Genzyme, Ultragenyx, Armagen, Alexion, Inventiva, PTC, Ciesi, and RegenXbio outside the submitted work.

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