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Impact of Elosulfase Alfa on Pain in Patients with Morquio A Syndrome over 52 Weeks: MOR-008: A Randomized, Double-Blind, Pilot Study

Marsha Treadwell[1], Paul R. Harmatz[1], Barbara K. Burton[2], John J. Mitchell[3], Nicole Muschol[4], Simon A. Jones[5], Gregory M. Pastores[6,7], Heather A. Lau[7], Rebecca Sparkes[8], V. Reid Sutton[9], Bianca Meesen[10], Christine A. Haller[11], Adam J. Shaywitz[11], and Jeffrey I. Gold[12,13]

Abstract

Patients with mucopolysaccharidosis (MPS), and Morquio A syndrome (MPS IVA) in particular, often report substantial pain burden. MOR-008 was a randomized, double-blind, pilot study assessing the safety and efficacy, including impact on patient-reported pain, of 52 weeks of treatment with elosulfase alfa (at a dose of 2.0 or 4.0 mg/kg/week) in patients with Morquio A syndrome (≥7 years old). Assessment of pain at baseline revealed that patients (N = 25) had a mean number of pain locations of 5.7, mean pain intensity score of 4.6 (indicative of medium pain), and a mean number of selected pain descriptors of 7.4 words. Treatment with elosulfase alfa improved subjective pain score (reduced to 3.2), pain locations (reduced by a mean of 1 location), and pain descriptor words (reduced to 4.9 words) over 1 year (52 weeks), suggesting that elosulfase alfa can reduce pain in some patients with Morquio A.

Keywords

mucopolysaccharidosis IVA, Morquio A syndrome, chronic pain, lysosomal storage diseases, galactosamine-6-sulfatase, enzyme replacement therapy, elosulfase alfa

[1] UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA
[2] Ann and Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[3] Montreal Children's Hospital, Quebec, Canada
[4] University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[5] Willink Unit, St. Mary's Hospital, CMFT, MAHSC, University of Manchester, Manchester, United Kingdom
[6] University College Dublin, Mater Misericordiae University Hospital, Dublin, Ireland
[7] New York University School of Medicine, New York, NY, USA
[8] Alberta Children's Hospital, Calgary, Alberta, Canada
[9] Baylor College of Medicine & Texas Children's Hospital, Houston, TX, USA
[10] Ismar Healthcare, Lier, Belgium
[11] BioMarin Pharmaceutical Inc., Novato, CA, USA
[12] Department of Anesthesiology, Pediatrics, and Psychiatry & Behavioral Sciences, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[13] Department of Anesthesiology Critical Care Medicine, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

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Corresponding Author:
Marsha Treadwell, UCSF Benioff Children's Hospital Oakland, 747 52nd St., Oakland, CA 94609, USA.
Email: mtreadwell@mail.cho.org

Introduction

The mucopolysaccharidosis (MPS) disorders are frequently associated with significant pain[1–7] caused by joint abnormalities, recurrent otitis media, neurological involvement, increased intracranial pressure, spinal cord compression, carpal tunnel syndrome, or a combination of these comorbidities.[1,5,8–10] Patients with MPS frequently use pain medication and may develop chronic pain that can affect physical functioning, activities of daily living, emotional and school functioning, and health-related quality of life (HRQoL).[2,11,12] In addition, the burden of pain has been found to have a substantial economic impact on society in terms of treatment costs and lost productivity.[13] Consequently, pain management is becoming an important component of care for patients with MPS.

Several studies have investigated pain as a clinical outcome in patients with MPS using patient (or caregiver)-reported questionnaires to measure individual patient's pain levels.[3–7,14–17] These multidimensional tools are described in Figure 1 and Appendix 1 and include the (Childhood) Health Assessment Questionnaire Pain scale (or a modified version),[3–7,14,15] the non-communicating Children's Pain Checklist–Revised, the six-face Faces Pain Scale–Revised, the Adolescent Pediatric Pain Tool (APPT), the Brief Pain Inventory short form, and a visual analog scale (VAS).[1,2] Results from 2 studies in patients with MPS (N = 55) and Morquio A (N = 63) using these questionnaires (Appendix 1) indicate that >60% of all patients with MPS experience joint pain.[1,2] The highest frequency of pain was observed in patients with MPS III, while the most severe pain intensity was reported by patients with Morquio A,[1] which is not unexpected, as the latter can have severe skeletal and joint abnormalities.[26]

Morquio A syndrome (MPS IVA; OMIM #253000) is a rare inherited progressive disorder[27] caused by a deficiency of the lysosomal enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS, EC 3.1.6.4) involved in the degradation of the glycosaminoglycans (GAGs) keratan sulfate and chondroitin-6-sulfate. The progressive accumulation of GAGs will interfere with normal cellular function, leading to growth impairment and increasing dysfunction of multiple organ systems in patients with Morquio A.[28–30] Musculoskeletal abnormalities, joint hypermobility, stiffness and pain, cardiorespiratory dysfunction, or a combination of these manifestations often lead to reduced mobility and endurance.[10,31–33] These increasing physical impairments coupled with a declining ability to perform activities of daily living may negatively impact the patient's quality of life, and many patients with Morquio A become wheelchair bound by their teen years.[2,31,32]

Weekly enzyme replacement therapy (ERT) infusions with elosulfase alfa, a recombinant form of human GALNS (Vimizim®; BioMarin Pharmaceutical Inc., Novato, California), is currently the only approved therapy for Morquio A syndrome.[34] In the pivotal phase 3 study (MOR 004, NCT01275066), patients receiving elosulfase alfa at a dose of 2.0 mg/kg/week demonstrated statistically significant improvement in endurance as measured by the 6-minute walk test (6MWT) distance and numerical improvements in 3-minute stair climb test (3MSCT) performance, respiratory function, activities of daily living, and height/growth at week 24 compared to those receiving placebo.[35,36] Improvements in 6MWT, 3MSCT, and respiratory function were sustained over 120 weeks in the long-term follow-up MOR 005 phase 3 extension study.[37,38] However, pain assessments were not performed in MOR-004/005.

In addition to the phase 3 study, a randomized, double-blind, pilot study (MOR-008, NCT01609062) assessed the safety and efficacy of 2 doses of elosulfase alfa (2.0 and 4.0 mg/kg/week; N = 25) over 24 weeks.[16] Safety was the primary outcome measure of MOR-008, with secondary efficacy end points including effects of ERT on endurance, exercise capacity, and pain. The baseline values for the 6MWT and 3MSCT in MOR-008 were higher than those seen in the phase 3 study,[35] due to study inclusion criteria that required a 6MWT distance of $\geq$200 m which was aimed at recruiting a population healthy enough to complete several of the efficacy measures. Results of the primary treatment phase (24 weeks) of MOR-008 were previously published. There was no change from baseline in 6MWT in both dosing groups and only a numerical change for 3MSCT in the 4.0 mg/kg/week group. A ceiling effect might potentially explain why 6MWT and 3MSCT outcomes remained essentially unchanged during the primary treatment phase of MOR-008.[16] The baseline pain intensity score on the Word Graphic Rating Scale (WGRS) of the APPT reported by patients with Morquio A in MOR-008 was 4.6 [16], which corresponds to "medium pain."[23] The mean pain intensity score numerically improved to 3.2 at week 24 of elosulfase alfa treatment, with a median % change of −30.6%.[16] Additional pain outcomes up to 52 weeks of treatment with elosulfase alfa are further explored in the present study.

Methods

Ethical Conduct of the Study

Review and approval of MOR-008 was obtained by the Institutional Review Board, Independent Ethics Committee, or Research Ethics Board at each participating center. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from each participant (or his or her legally authorized representative) before entering the study.

Study Design and Participants

MOR-008 was a multinational, multicenter, randomized, phase 2, double-blind pilot study investigating the safety and physiological effects of 2 doses of elosulfase alfa in patients with Morquio A syndrome. Inclusion and exclusion criteria and study design of the primary treatment phase have been described previously.[16] Briefly, patients $\geq$7 years and able to walk $\geq$200 m in the 6MWT at screening were randomized to receive elosulfase alfa 2.0 or 4.0 mg/kg/wk for 27 weeks. Primary end points were safety and tolerability of both doses;

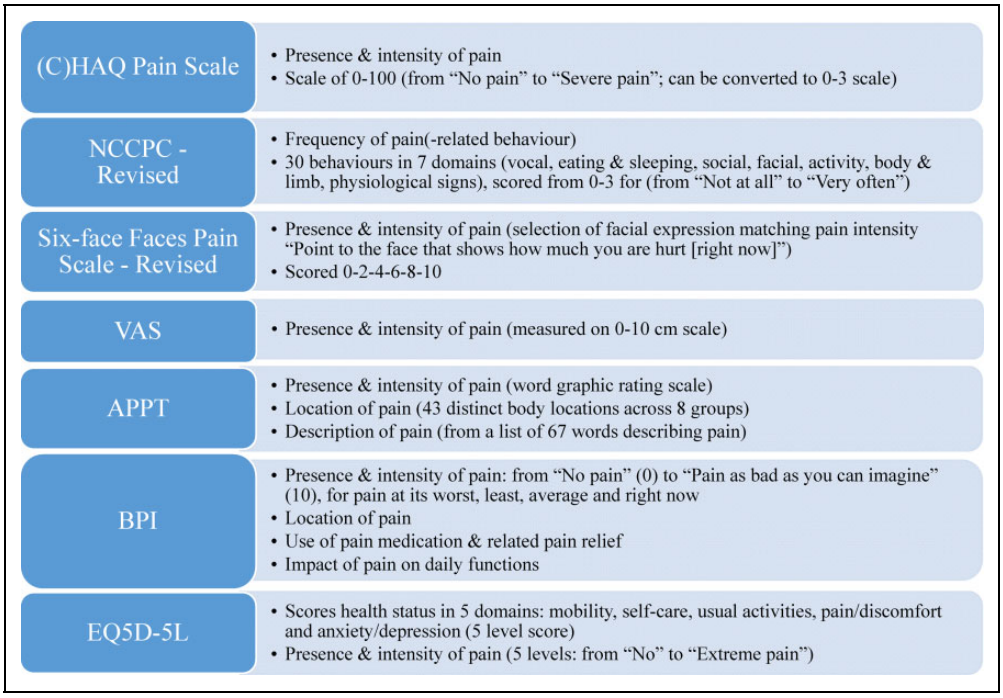

Figure 1. Questionnaires reported in the literature for pain assessment in MPS. Several questionnaires can be used when assessing pain in patients with MPS. There are differences in the dimensions and amount of information they capture about the experienced pain. (C)HAQ, (Childhood) Health Assessment Questionnaire[18–20]; NCCPC, Non-communicating Children's Pain Checklist[21]; six-face Faces Pain Scale–Revised[22]; VAS, Visual Analog Scale[1]; APPT, Adolescent Pediatric Pain Tool; WGRS, word graphic rating scale[23]; BPI, Brief Pain Inventory[24]; EQ5D-5 L, EuroQoL 5 Domains 5 Levels.[25]

secondary end points included effects of elosulfase alfa on endurance, exercise capacity, respiratory function, muscle strength, cardiac function, pain, urinary keratan sulfate levels, and pharmacokinetic parameters. Patients who completed the primary treatment phase were enrolled in the extension phase, during which they received the same dose of elosulfase alfa as during the primary treatment phase through week 52.

Pain Assessment

Pain experienced in the last 24 hours was measured using the APPT at screening and at weeks 12, 24, and 52 following endurance tests (if they occurred at the same visit). The APPT is a validated, multidimensional tool to evaluate pain in children, adolescents, and young adults (Figure 2A).[23] In the first part of the APPT, a body diagram with 43 distinct body locations distributed across 8 groups is used to indicate the location of pain. In the second part, pain intensity is measured on a 10-cm VAS, i.e. the WGRS, including "no pain" (0 cm), "little pain" (2.5 cm), "medium pain" (5.0 cm), "large pain" (7.5 cm), and "worst possible pain" (10 cm). In the last part of the APPT, a list of 67 words is provided for the patient to select words that describe the pain. Words are divided in 4 pain descriptor categories: sensory, affective, evaluative, and temporal.[23] Some younger patients or those that preferred to, used a Faces Pain Scale instead of the WGRS to measure pain intensity at baseline. The Faces Pain Scale asks patients to select from 6 facial expressions the one that best reflects their pain (Figure 2B) and corresponds to a score that ranges from 0 (no pain) to 10 (very much pain).[22]

Statistical Methods

Efficacy analyses were performed on the modified intent-to-treat population, consisting of all patients randomized to study treatment that received at least 1 dose of study drug and had at least 1 post-treatment observation. The analyses were performed on the total study population (i.e., the two dosing groups combined), but results are also presented separately. Descriptive statistics including sample size, mean, standard deviation (SD), percentage, median, and interquartile ranges (IQR), when appropriate, were generated. Key comparisons for outcomes were within the same patient for parameters measured at screening and weeks 24 and 52. Values obtained at screening (days −21 to −1) were used as baseline measures.

Results

Patient Characteristics

Twenty-five patients were randomized to elosulfase alfa 2.0 mg/kg/week (N = 15) or 4.0 mg/kg/week (N = 10). Demographics and baseline characteristics (Appendix 2) for the total study population have been published previously.[16] All 25 patients completed the primary treatment phase and were enrolled in the extension study (Appendix 3). One patient

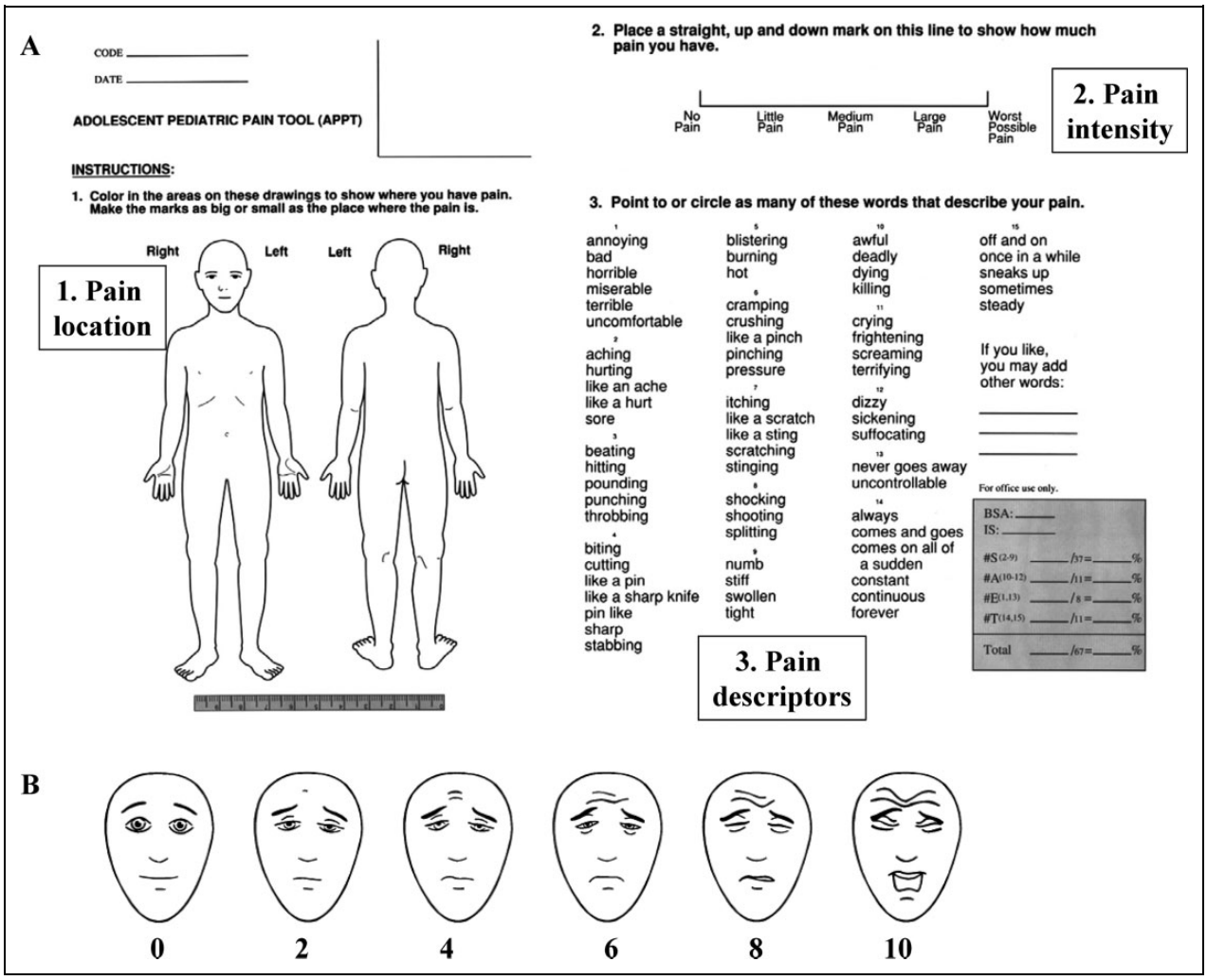

Figure 2. A, The adolescent pediatric pain tool. B, The faces pain scale. The adolescent pediatric pain tool is a validated, multidimensional tool to evaluate pain in children, adolescents, and young adults. It consists of three different parts. In the first part, pain location can be indicated on a body diagram. In the second part, pain intensity is measured on a 10-cm visual analog scale. In the last part, pain descriptors can be selected from a list of 67 words (reproduced from Jacob EA, et al. Pain Management Nursing 2014,[23] with kind permission from Elsevier). The faces pain scale allows patients to select out of 6 facial expressions the face that best corresponds to their pain, ranging from "no pain" (score of 0) to "very much pain" (score of 10) (reproduced from Hicks CL, et al Pain 2001,[22] Faces pain Scale–Revised (FPS-R). www.iasp-pain.org/fpsr. Copyright ©2001, International Association for the Study of Pain. Reproduced with permission).

continued through week 52 but did not receive infusions of elosulfase alpha after week 24 due to relocation away from the study site. Another patient discontinued prior to week 52 (last infusion at week 39) due to a planned surgery and transition to an expanded access program at a site closer to her place of residence.

APPT Outcomes

At baseline, all patients reported at least 1 pain location. Pain was most frequently experienced in the lower extremities (68% of patients), followed by the head and neck areas (32% of all patients), and the upper extremities (32% of patients). After 52 weeks of elosulfase alfa treatment, the lower extremities were still the most frequently reported location of pain in the total study population (76%).

Elosulfase alfa treatment was associated with a mean (SD) decrease of 1.3 (4.1) and 1.0 (5.2) in the number of pain locations from baseline to week 24 and 52, respectively, in the total study population (Figure 3A, Table 1). The decrease in number of pain locations was seen only in the 2.0 mg/kg/week group. The number of pain locations reported by the 4.0 mg/kg/week group remained stable; however, the mean number of pain locations at baseline was already lower in this group (Table 1).

The mean baseline pain intensity score on the WGRS was 4.6 (median score 4.9), corresponding to categorical scores of "medium pain." Mean and median scores at baseline were slightly worse (approximately 1 point higher) in the 2.0 mg/kg/week group compared to the 4.0 mg/kg/week group (Table 2); this imbalance between the 2 dose groups at baseline, despite randomization, may (at least partly) be due to the small sample

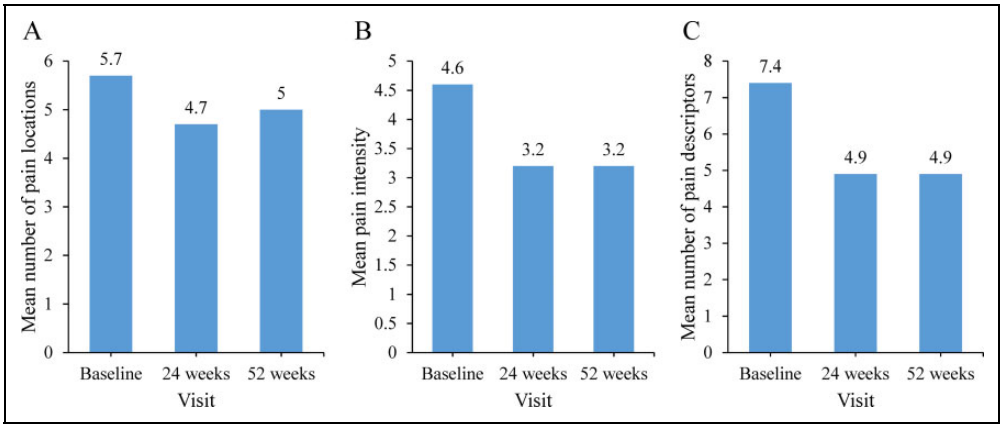

Figure 3. Mean number of pain locations (A), pain intensity (B) and pain descriptors (C) decreased from baseline to week 52 after treatment with elosulfase alfa in the total study population. Modified intent-to-treat population analysis of the total study population (i.e., 2.0 mg/kg/week and 4.0 mg/kg/week treatment groups combined).

Table 1. Impact of Elosulfase Alfa on Number of Pain Locations. Number of Pain Locations Reported Per Patient in the Adolescent Pediatric Pain Tool at Baseline and after Treatment with Elosulfase Alfa for 24 and 52 Weeks. Modified Intent-to-Treat Population Analysis of 2.0 and 4.0 mg/kg/week Groups and the Total Study Population.

Timepoint	2.0 mg/kg/wk		4.0 mg/kg/wk		Total Study Population	
Baseline	N		N		N	
Mean (SD)	12	7.2 (4.5)	9	3.7 (2.7)	21	5.7 (4.1)
Median (IQR)	12	6.0 (3, 12)	9	2.0 (2, 5)	21	5.0 (2, 9)
Week 24						
Mean (SD)	15	5.5 (4.7)	10	3.5 (2.4)	25	4.7 (4.0)
Mean (SD) change from baseline	12	−2.2 (4.8)	9	−0.1 (2.8)	21	−1.3 (4.1)
Median (IQR)	15	5.0 (1, 9)	10	3.0 (2, 6)	25	3.0 (2, 6)
Median change from baseline (IQR)	12	−2.0 (−5, 2)	9	1.0 (−1, 1)	21	0.0 (−4, 1)
Week 52						
Mean (SD)	14	6.1 (6.8)	10	3.4 (3.1)	24	5.0 (5.7)
Mean (SD) change from baseline	11	−1.8 (6.4)	9	0.0 (3.2)	20	−1.0 (5.2)
Median (IQR)	14	3.0 (1, 10)	10	3.0 (1, 3)	24	3.0 (1, 8)
Median change from baseline (IQR)	11	−1.0 (−5, 0)	9	1.0 (−3, 1)	20	0.0 (−4, 1)

Abbreviations: SD, standard deviation; IQR, interquartile range.

size. Results of the primary treatment phase showed that elosulfase alfa treatment for 24 weeks reduced the pain intensity score by 1.8 (SD 3.3) in the total study population, corresponding to a median % change of −30.6%, as previously reported.[16] After 52 weeks of treatment, this reduction was less apparent: The mean pain intensity score of the total population changed by −0.8 (SD 3.2) from baseline (Figure 3B), the median change was 0.1 (IQR −2.3, 1.4), corresponding to a median % change of 1.7% (IQR −61.5, 38.9; Table 2). When separating the treatments, both groups showed a similar mean reduction of 0.8, but only the 4.0 mg/kg/week group showed a median reduction in pain intensity score (−0.2 [−1.0, 1.0]). Data from individual patients show improved or stable pain intensity scores throughout the study period in the majority of patients (Figure 4).

At baseline, the mean and median number of words selected by the total study population to describe pain was 7.4 (SD 4.2) and 7.0 (IQR 4, 10), respectively, of a total of 67 words and were primarily sensory and temporal pain descriptors (mean number of words were 3.5 and 2.0, respectively). Patients in the 2.0 mg/kg/week group selected a higher number of words to describe pain compared with patients in the 4.0 mg/kg/week group (Table 3). There was a mean change from baseline in the number of word descriptors in the total study population of −2.3 (SD 4.7) at week 24 and −1.7 (SD 5.9) at week 52 (Figure 3C) of elosulfase alfa treatment; median change in the total study population was −1.0 for both time points (Table 3). Patients selected primarily sensory and temporal pain descriptors (mean number of words were 2.2 and 1.7, respectively) at week 52.

Table 2. Impact of Elosulfase Alfa on Pain Intensity. The Pain Intensity Reported Per Patient at the Word Graphic Rating Scale of the Adolescent Pediatric Pain Tool at Baseline and after Treatment with Elosulfase Alfa for 52 Weeks. Modified Intent-to-Treat Population Analysis of 2.0 and 4.0 mg/kg/week Groups and the Total Study Population.

Timepoint	2.0 mg/kg/wk		4.0 mg/kg/wk		Total Study Population	
Baseline	N		N		N	
Mean (SD)	12	5.0 (2.9)	9	4.1 (2.5)	21	4.6 (2.7)
Median (IQR)	12	5.3 (3.3, 7.2)	9	4.5 (2.5, 5.0)	21	4.9 (3.0, 6.0)
Week 24						
Mean (SD)	15	3.2 (2.4)	9	3.0 (1.7)	24	3.2 (2.1)
Mean (SD) change from baseline	12	−2.2 (3.7)	8	−1.2 (2.9)	20	−1.8 (3.3)
Median (IQR)	15	3.6 (0.4, 5.3)	9	2.9 (2.2, 4.7)	24	3.0 (2.1, 5.1)
Median change from baseline (IQR)	12	−0.7 (−3.9, 0)	8	−0.7 (−3.1, 1.1)	20	−0.7 (−3.5, 0.1)
Week 52						
Mean (SD)	14	3.4 (3.0)	10	2.9 (2.2)	24	3.2 (2.6)
Mean (SD) change from baseline	11	−0.8 (3.4)	9	−0.8 (3.0)	20	−0.8 (3.2)
Median (IQR)	14	2.8 (0.5, 6.0)	10	2.8 (1.0, 4.0)	24	2.8 (0.8, 5.1)
Median change from baseline (IQR)	11	0.1 (−4.0, 1.4)	9	−0.2 (−1.0, 1.0)	20	0.1 (−2.3, 1.4)

Abbreviations: SD, standard deviation; IQR, inter-quartile range.

Discussion

The few clinical studies to date that have evaluated pain in MPS disorders indicate that a large proportion of patients have mild to moderate pain.[3–7,39] Approximately 40% of the patients with MPS report a pain score above the cut-off for significant pain and those with Morquio A syndrome (MPS IVA) experience the most severe pain.[1] Pain appears to significantly interfere with activities of daily living and negatively affect quality of life in patients with Morquio A.[2] These observations underscore the need for a treatment that can decrease pain burden in these patients. ERT has been approved for several lysosomal storage disorders, including MPS I,[3,40] MPS II,[41] MPS VI,[15,33] and MPS IVA/Morquio A.[34] In addition to the positive effect on endurance, ERT has been reported to reduce pain in patients with MPS I[3] and MPS VI[6,7,14,17] (Appendix 1). Less is known about the effect of ERT on pain in patients with Morquio A.[16]

Patients with Morquio A in the MOR-008 study reported a significant baseline level of pain in multiple body sites, with a predominance of pain in the lower extremities. The mean reported pain intensity score corresponded with "medium pain" on the APPT scale, consistent with pain locations and scores reported in the Morquio A patient-reported outcomes survey by Hendriksz et al.[2] Treatment with elosulfase alfa resulted in a decrease in subjective pain scores from baseline to weeks 24 and 52. The number of pain locations and word descriptors selected to describe pain decreased at both time points. After 24 weeks of treatment, the mean pain intensity score had decreased by a mean of 1.3 points on the 0 to 10-point rating scale in the total study population. There was still a numerical mean change from baseline in pain intensity score through week 52, although long-term treatment did not lead to greater pain reduction.

A recent study of 153 adolescents with chronic pain identified a raw change of 1 point on a 0 to 10-point numerical rating scale as the minimal clinically important difference for pain intensity, corresponding to a change of −12.5%.[42] Although the adolescents in this study were not patients with Morquio A, they showed several relevant similarities with the MOR-008 patient population, with a mean age of 15.5 years (vs 13.7 years in MOR-008) and main pain locations being the head (56%) and back/extremities (25%) versus the head and neck area (32%) and the extremities (lower 68% and upper 32%) in MOR-008. The reduction in pain intensity observed in the primary treatment phase of MOR-008 was >1 point for most patients and the mean reduction in the extension phase approximates a change of 1, suggesting that the observed effect on pain intensity approaches what is considered to be clinically important. Patients who did not show an improvement in pain intensity mostly presented with stable scores. This suggests that their pain did not worsen as could be expected after a 1-year-long period in a progressive disease such as Morquio A.[2,31]

The mechanism of action responsible for elosulfase alfa treatment-associated pain control is not readily apparent and may involve many factors. Data from animal studies suggest a GAG-mediated apoptosis of articular chondrocytes as well as a GAG-mediated inflammatory component, operating through the toll-like receptor 4 pathway, to the musculoskeletal disease in MPS,[43–46] as observed in rheumatoid arthritis.[47] Hence, one of the pain-controlling mechanisms of elosulfase alfa may function via decreasing the GAG accumulation in macrophages throughout the tissues.[30] This could reduce inflammatory responses at the articular surfaces and as a result improve joint pain and stiffness. In addition, studies in MPS VI and VII animal models have shown that treatment with anti-inflammatory drugs reduces the GAG-mediated apoptotic and inflammatory component in

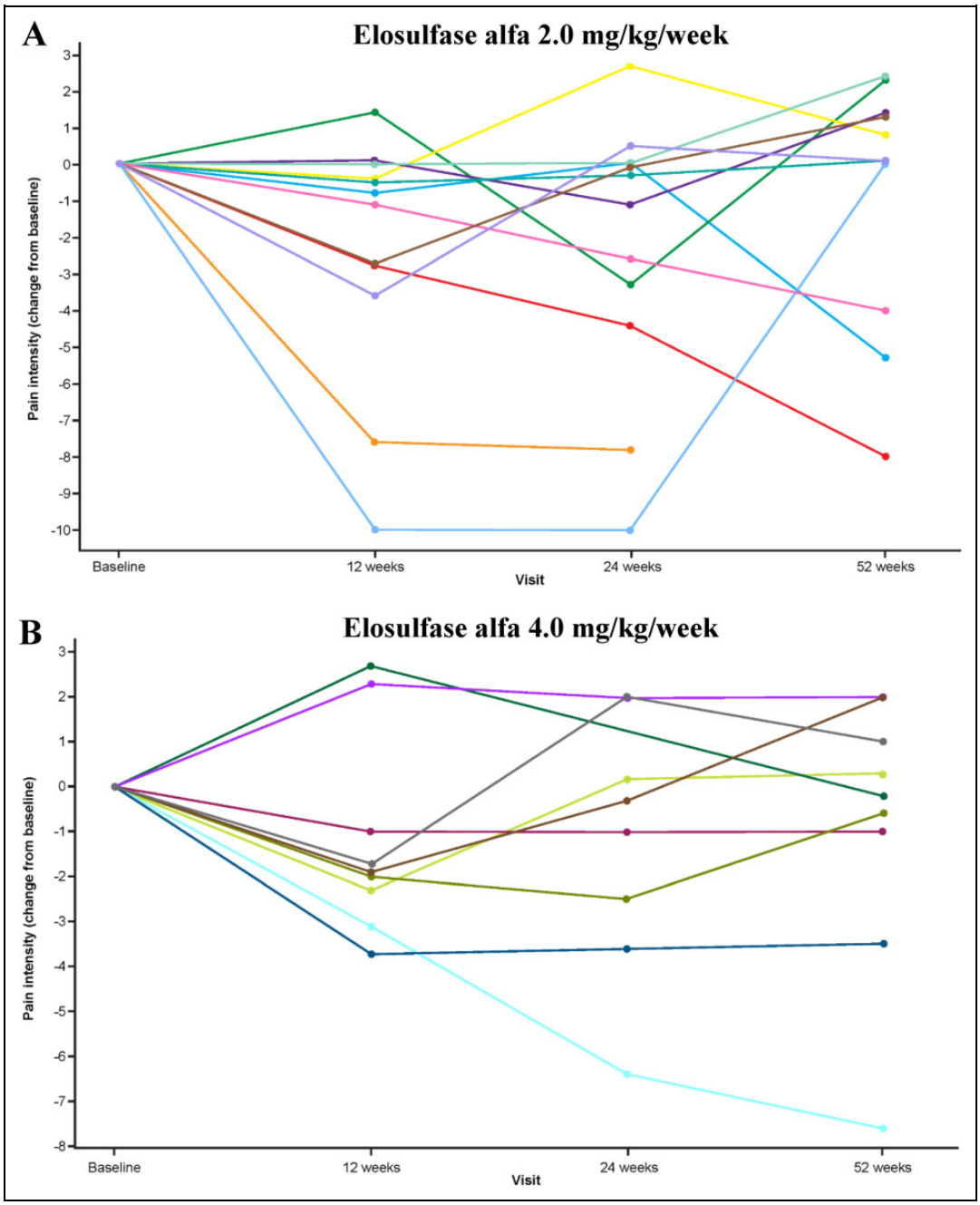

Figure 4. Pain intensity change from baseline: data of individual patients. Change from baseline in pain intensity on the word graphic rating scale (WGRS) in elosulfase alfa 2.0 mg/kg/week (A) and 4.0 mg/kg/week (B) treatment groups. Different lines represent different patients. Modified intent-to-treat analysis set. A negative value for the change from baseline in pain intensity on the WGRS represents an improvement in pain intensity, while a positive value represents a worsening in pain intensity.

articular and synovial tissue and enhances the positive effect of ERT on articular tissue and motor activity when combined.[45,46] These results suggest that ERT in combination with anti-inflammatory treatment may have beneficial effects on joint pain in patients with Morquio A. However, additional research in this area is needed to assess this hypothesis.

In addition to the physical relief of the pain sensation itself, a reduction in pain may also improve HRQoL, given that chronic pain can influence different aspects of normal daily life and cause psychological distress.[12,48] Two studies by Gold et al. showed that there is a negative relationship between chronic pain and HRQoL in children and adolescents: HRQoL scores were worse when pain intensity and frequency were higher.[11,12] Additionally, results of an international Morquio A patient-reported outcomes survey demonstrate that HRQoL is primarily related to the patient's ability to remain independently mobile and that patients tolerate more pain during activities of daily living if they are able to remain more mobile or

Table 3. Impact of Elosulfase Alfa on Pain Descriptors. Number of Pain Descriptors Selected (from a Total of 67 Words) in the Adolescent Pediatric Pain Tool at Baseline and after Treatment with Elosulfase Alfa for 24 and 52 Weeks. Modified Intent-to-Treat Population Analysis of 2.0 and 4.0 mg/kg/week Groups and the Total Study Population.

Timepoint	2.0 mg/kg/wk		4.0 mg/kg/wk		Total Study Population	
Baseline	N		N		N	
Mean (SD) number of words	11	8.0 (5.2)	9	6.6 (2.5)	20	7.4 (4.2)
Median (IQR) number of words	11	8.0 (4, 14)	9	6.0 (4, 8)	20	7.0 (4, 10)
Week 24						
Mean (SD) number of words	15	5.3 (4.3)	10	4.3 (3.9)	25	4.9 (4.1)
Mean (SD) change from baseline in number of words	11	−2.5 (5.6)	9	−1.9 (3.6)	20	−2.3 (4.7)
Median (IQR) number of words	15	6.0 (1, 8)	10	4.0 (1, 6)	25	5.0 (1, 7)
Median (IQR) change from baseline in number of words	11	−1.0 (−4, 1)	9	−1.0 (−5, 1)	20	−1.0 (−5, 1)
Week 52						
Mean (SD) number of words	14	5.6 (5.3)	10	4.0 (2.6)	24	4.9 (4.3)
Mean (SD) change from baseline in number of words	10	−1.0 (7.9)	9	−2.4 (2.7)	19	−1.7 (5.9)
Median (IQR) number of words	14	5.0 (1, 7)	10	3.0 (3, 7)	24	3.5 (2, 7)
Median (IQR) change from baseline in number of words	10	0.5 (−6, 2)	9	−3.0 (−4, −1)	19	−1.0 (−5, 1)

Abbreviations: SD, standard deviation; IQR, inter-quartile range.

use their wheelchair less frequently.[2] In addition, fatigue was shown to be a significant problem in patients suffering from chronic pain, as it functions as an intermediary between pain and the overall HRQoL.[11] Children and adult patients with Morquio A frequently report fatigue or low stamina and this is influenced by the use of a wheelchair.[2] Again, better mobility showed a negative correlation with fatigue, following the same pattern as for pain.[2] These findings highlight the negative effects of chronic pain on daily living activities and emphasize the need for intervention protocols that help manage pain and promote increased functioning of patients with Morquio A. The decrease in pain burden reported in MOR 008 may contribute to improvements in HRQoL in this Morquio A population. Future studies on the effect of ERT in patients with Morquio A should further explore the relationship between pain management, HRQoL, fatigue, and other functional outcomes.

Limitations of this pilot study should be taken into account when interpreting these results. Study inclusion criteria led to recruitment of a relatively healthy population, which may have resulted in a ceiling effect for some efficacy outcome measures. Moreover, this study was not powered to show statistically significant differences between dose groups. As there was no placebo group, we do not know whether untreated patients would have declined in some or all pain assessments during the study period. Additionally, concomitant pain medication use was not rigorously monitored and may not have been consistent throughout the study. Finally, pain is a complex experience and its perception is influenced by cognitive and emotional factors.[49] Conversely, the circuitry that is responsible for the psychological modulation of pain can be affected by chronic pain, leading to changes in emotional and cognitive domains. As a result, the context and meaning of pain influence its perception by the patient, which leads to large inter-individual as well as intra-individual differences in pain perception.[49] Despite these limitations, this study gathered pilot data in order to increase the current understanding of pain in patients with Morquio A and how treatment with elosulfase alfa influences these impairments and to generate hypotheses for potential future studies.

Conclusion

MOR-008 is the first clinical study to measure the impact of ERT with elosulfase alfa on pain burden in patients with Morquio A syndrome. MOR-008 patients reported a baseline pain level of medium intensity at multiple body sites, with a predominance of pain locations in the lower extremities. Improvements in perceived burden of pain were reported after treatment with elosulfase alfa over 24 and 52 weeks.

Appendix 1

Table A1. Overview of the Studies that Evaluated Pain (Burden) in Patients with MPS.[a]

Questionnaire	MPS Type	Number of Subjects; Age Range	ERT (duration)	Baseline Pain Intensity score	Final Pain Intensity Score	Reference
(C)HAQ (0-3 scale)	MPS I	N = 45; 6.3-43.3 years	Laronidase (3.5-4 years)	0.93 (N = 30)	0.56 (N = 30)	3
(C)HAQ (0-100 scale)	MPS II	N = 96; 5-30.9 years	Not used	28.2		4
	MPS VI	N = 90; 4-18 years	Not used	31.6		5
		N = 28; 19-56 years	Not used	38.2		5
		N = 22; 4-18 years	Galsulfase (±6.8 years)	24.3	31.9	6
		N = 10; >18 years	Galsulfase (±6.8 years)	35.5	22.3	6
		N = 10; 6-22 years	Galsulfase (48 weeks)	41	55% reduction	7
		N = 9; 1.4-21.1 years	Galsulfase (2 years)	NA	30.5% reduction	17
NCCPC–Revised (0-90 scale)	MPS	N = 35; <8 years or with intellectual disability	Not used	Range 0-36 (cut-off for pain of 7 in 45.7%)		1
Six-face Faces Pain Scale–Revised (0-100 scale)	MPS	N = 11; 8-18 years without intellectual disability	Not used	Range 0-92 (cut-off for moderate pain of 45 in 18.1%)		1
VAS (0-100 scale)	MPS	N = 8; >18 years without intellectual disability	Not used	Range 10-88, median 41.5 (cut-off for moderate pain of 45 in 37.5%)		1
BPI (0-10 scale)	MPS IV	N = 19; 18-67 years	Not used	4.39		39
	MPS IVA	N = 27; ≥ 18 years	Not used	No WC: 1.69 (N = 4) WC when needed: 3.55 (N = 14) WC always used: 2.69 (N = 9)		2
APPT (0-10 scale)	MPS IVA	N = 36; 5-17 years	Not used	No WC: 4.38 (N = 20) WC when needed: 4.00 (N = 14) WC always used: 1.00 (N = 2)		2
	MPS IVA	N = 25; 8-40 years	Elosulfase alfa (52 weeks)	Pain intensity: 4.6	Pain intensity: 3.2	MOR-008 study

Abbreviations: APPT, Adolescent Pediatric Pain Tool; BPI, Brief Pain Inventory; (C)HAQ, (Childhood) Health Assessment Questionnaire; NA, not available; NCCPC, noncommunicating Children's Pain Checklist; six-face Faces Pain Scale–Revised; VAS, Visual Analog Scale; WC: wheelchair.

[a]Summary of the observed pain (burden) in patients with MPS. Overview of the study population, whether they were treated with ERT, and the pain questionnaire used in the study. For the (C)HAQ the 0-100 pain scale was used, unless mentioned otherwise.

Appendix 2

Table A2. Demographics and Baseline Characteristics (Intent-to-Treat Population).

	2.0 mg/kg/week (N = 15)	4.0 mg/kg/week (N = 10)	Total Study Population (N = 25)
Age at enrollment, years			
Mean (SD)	14.9 (9.3)	12.0 (3.2)	13.7 (7.5)
Median (IQR)	11.3 (9, 17)	12.2 (9, 14)	11.5 (9, 15)
Sex, n			
Female	12	4	16
Male	3	6	9
Race, n			
White	14	9	23
Other	1	1	2
6MWT, m			
Mean (SD)	369.6 (89.2)	376.3 (70.0)	372.2 (80.6)
Median (IQR)	346.8 (300, 422)	393.2 (326, 444)	372.3 (321, 422)
3MSCT, stairs/min			
Mean (SD)	65.5 (21.4)	64.2 (23.3)	65.0 (21.7)
Median (IQR)	65.3 (55, 72)	63.6 (53, 84)	65.2 (55, 78)

Abbreviations: IQR, interquartile range; MSCT, 3-minute stair climb test; SD, standard deviation; 6MWT, 6-minute walk test.

Appendix 3

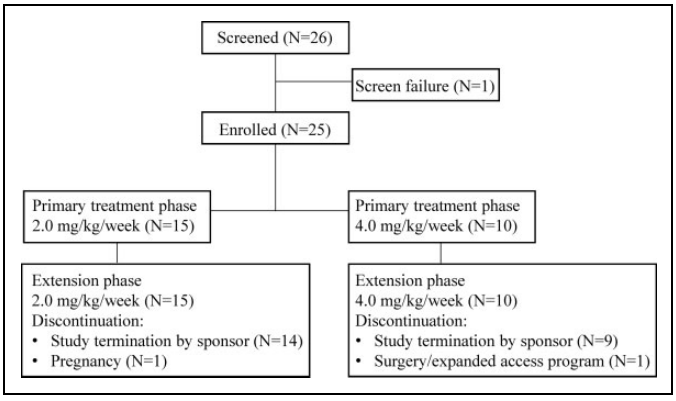

Figure A1. CONSORT flow diagram.

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Authors' Contributions

MT was consultant to the study, designed the plan for the pain assessment strategies used in the present study, scored and interpreted the pain assessments, and reviewed data analyses. PRH, BKB, JJM, NM, SAJ, GMP, HAL, RS, and VRS were all primary investigators of this study, contributed to the planning of the study, were involved in the clinical examinations and collection of data. JIG provided insight in the interpretation of the data. CH and AJS assisted with conduction of the study, data analyses, and development of the manuscript. All authors contributed to the writing and critical review of the manuscript and approved the final manuscript.

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References

1. Brands MMG, Güngör D, van den Hout JMP, et al. Pain: a prevalent feature in patients with mucopolysaccharidosis. Results of a cross-sectional national survey. *J Inherit Metab Dis*. 2015; 38(2):323-331.
2. Hendriksz CJ, Lavery C, Coker M, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. *Orphanet J Rare Dis*. 2014;9:32.
3. Clarke LA, Wraith JE, Beck M, et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. *Pediatrics*. 2009;123(1):229-240.
4. Raluy-Callado M, Chen WH, Whiteman DAH, Fang J,, Wiklund I. The impact of Hunter syndrome (mucopolysaccharidosis type II) on health-related quality of life. *Orphanet J Rare Dis*. 2013; 8(1):101.
5. Swiedler SJ, Beck M, Bajbouj M, et al. Threshold effect of urinary glycosaminoglycans and the walk test as indicators of disease progression in a survey of subjects with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *Am J Med Genet*. 2005; 134A(2):144-150.
6. Giugliani R, Lampe C, Guffon N, et al. Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)-10-year follow-up of patients who previously participated in an MPS VI survey study. *Am J Med Genet A*. 2014;164A(8):1953-1964.
7. Harmatz P, Ketteridge D, Giugliani R, et al. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. *Pediatrics*. 2005;115(6): e681-e689.
8. White K, Kim T, Neufeld JA. Clinical assessment and treatment of carpal tunnel syndrome in the mucopolysaccharidoses. *J Pediatr Rehabil Med*. 2010;3(1):57-62.
9. The MPS Society: Diseases: Downloads and resources. http://www.mpssociety.org.uk/en/diseases/downloads-resources/. Accessed June, 2017.
10. Lampe C, Bellettato CM, Karabul N, Scarpa M. Mucopolysaccharidoses and other lysosomal storage diseases. *Rheum Dis Clin North Am*. 2013;39(2):431-455.
11. Gold JI, Mahrer NE, Yee J, Palermo TM. Pain, fatigue, and health-related quality of life in children and adolescents with chronic pain. *Clin J Pain*. 2009;25(5):407-412.
12. Gold JI, Yetwin AK, Mahrer NE, et al. Pediatric chronic pain and health-related quality of life. *J Pediatr Nurs*. 2009;24(2):141-150.
13. Institute of Medicine (US). *Relieving Pain in America*. Washington, DC: National Academies Press; 2011.
14. Harmatz P, Whitley CB, Waber L, et al. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *J Pediatr*. 2004;144(5):574-580.
15. Harmatz P, Giugliani R, Schwartz I, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J Pediatr*. 2006;148(4):533-539.
16. Burton BK, Berger KI, Lewis GD, et al. Safety and physiological effects of two different doses of elosulfase alfa in patients with Morquio A syndrome: A randomized, double-blind, pilot study. *Am J Med Genet A*. 2015;167A(10):2272-2281.
17. Lin HY, Chen MR, Chuang CK, et al. Enzyme replacement therapy for mucopolysaccharidosis VI-experience in Taiwan. *J Inherit Metab Dis*. 2010;33(suppl 3):S421-S427.
18. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum*. 1994;37(12):1761-1769.
19. National Institute of Environmental Health Sciences. The Health Assessment Questionnaire (HAQ) Disability Index (DI) of the Clinical Health Assessment Questionnaire (version 96.4) https://www.niehs.nih.gov/research/resources/assets/docs/haq_instructions_508.pdf. Accessed June, 2017.
20. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health Quality Life Outcomes*. 2003;1:20.
21. Breau LM, McGrath PJ, Camfield CS, Finley GA. Psychometric properties of the non-communicating children's pain checklist-revised. *Pain*. 2002;99(1-2):349-357.
22. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain*. 2001;93(2): 173-183.
23. Jacob E, Mack AK, Savedra M, Van Cleve L, Wilkie DJ. Adolescent pediatric pain tool for multidimensional measurement of pain in children and adolescents. *Pain Manag Nurs*. 2014;15(3): 694-706.

24. The Brief Pain Inventory: MD Anderson Cancer Society. http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html. Accessed June, 2017.
25. EuroQoL: EQ-5D-5 L User guide (version 2.1) 2015. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf. Accessed June, 2017.
26. Hendriksz CJ, Harmatz P, Beck M, et al. Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA. *Mol Genet Metab*. 2013;110(1-2):54-64.
27. Leadley RM, Lang S, Misso K, et al. A systematic review of the prevalence of Morquio A syndrome: challenges for study reporting in rare diseases. *Orphanet J Rare Dis*. 2014;9:173.
28. Tomatsu S, Montaño AM, Oikawa H, et al. Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment. *Curr Pharm Biotechnol*. 2011;12(6):931-945.
29. Montaño AM, Tomatsu S, Gottesman GS, Smith M, Orii T. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. *J Inherit Metab Dis*. 2007;30(2):165-174.
30. Yasuda E, Fushimi K, Suzuki Y, et al. Pathogenesis of Morquio A syndrome: an autopsied case reveals systemic storage disorder. *Mol Genet Metab*. 2013;109(3):301-311.
31. Harmatz P, Mengel KE, Giugliani R, et al. The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects. *Mol Genet Metab*. 2013;109(1):54-61.
32. Hendriksz CJ, Al-Jawad M, Berger KI, et al. Clinical overview and treatment options for non-skeletal manifestations of mucopolysaccharidosis type IVA. *J Inherit Metab Dis*. 2013;36(2):309-322.
33. Muenzer J. Overview of the mucopolysaccharidoses. *Rheumatology (Oxford)*. 2011;50(suppl 5):v4-v12.
34. Sanford M, Lo JH. Elosulfase alfa: first global approval. *Drugs*. 2014;74(6):713-718.
35. Hendriksz CJ, Burton B, Fleming TR, et al. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. *J Inherit Metab Dis*. 2014;37(6):979-990.
36. Hendriksz CJ, Giugliani R, Harmatz P, et al. Multi-domain impact of elosufase alfa in Morquio A syndrome in the pivotal phase III trial. *Mol Genet Metab*. 2015;114(2):178-185.
37. Hendriksz CJ, Parini R, AlSayed MD, et al. Long-term endurance and safety of elosulfase alfa enzyme replacement therapy in patients with Morquio A syndrome. *Mol Genet Metab*. 2016;119(1-2):131-143.
38. Hendriksz CJ, Berger KI, Parini R, et al. Impact of long-term elosulfase alfa treatment on respiratory function in patients with Morquio A syndrome. *J Inherit Metab Dis*. 2016;39(6):839-847.
39. Ali N, Cagle S. Psychological health in adults with Morquio syndrome. *JIMD Rep*. 2015;20:87-93.
40. Wraith JE, Clarke LA, Beck M, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human a-L-iduronidase (laronidase). *J Pediatr*. 2004;144(5):581-588.
41. Muenzer J, Wraith JE, Beck M, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). *Genet Med*. 2006;8(8):465-473.
42. Hirschfeld G, Wager J, Schmidt P, Zernikow B. Minimally clinically significant differences for adolescents with chronic pain - variability of ROC-based cut points. *J Pain*. 2014;15(1):32-39.
43. Simonaro CM, D'Angelo M, He X, et al. Mechanism of glycosaminoglycan-mediated bone and joint disease: implications for the mucopolysaccharidoses and other connective tissue diseases. *Am J Pathol*. 2008;172(1):112-122.
44. Simonaro CM. Cartilage and chondrocyte pathology in the mucopolysaccharidoses: the role of glycosaminoglycan-mediated inflammation. *J Pediatr Rehabil Med*. 2010;3(2):85-88.
45. Simonaro CM, Ge Y, Eliyahu E, He X, Jepsen KJ, Schuchman EH. Involvement of the Toll-like receptor 4 pathway and use of TNF-a antagonists for treatment of the mucopolysaccharidoses. *Proc Natl Acad Sci USA*. 2010;107(1):222-227.
46. Eliyahu E, Wolfson T, Ge Y, Jepsen KJ, Schuchman EH, Simonaro CM. Anti-TNF-alpha therapy enhances the effects of enzyme replacement therapy in rats with mucopolysaccharidosis type VI. *PLoS One*. 2011;6(8):e22447.
47. Wang JY, Roehrl MH. Glycosaminoglycans are a potential cause of rheumatoid arthritis. *Proc Natl Acad Sci USA*. 2002;99(22):14362-14367.
48. Palermo TM. Assessment of chronic pain in children: current status and emerging topics. *Pain Res Manag*. 2009;14(1):21-26.
49. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci*. 2013;14(7):502-511.