Molecular Genetics and Metabolism 123 (2018) 127–134

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Regular Article

Impact of long-term elosulfase alfa on activities of daily living in patients with Morquio A syndrome in an open-label, multi-center, phase 3 extension study

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ARTICLE INFO

Keywords:
Morquio A syndrome
MPS IVA
Elosulfase alfa
Disability
Activities of daily living
Enzyme replacement therapy

ABSTRACT

Background: Long-term safety and efficacy of elosulfase alfa enzyme replacement therapy (ERT) were assessed in 173 patients with Morquio A syndrome (mucopolysaccharidosis IVA) in a 96-week, open-label, multi-center, phase 3 extension study (MOR-005) of the pivotal 24-week, placebo-controlled study (MOR-004). Changes in efficacy endpoints were evaluated over 120 weeks, from MOR-004 baseline to MOR-005 week 96. We report the impact of ERT on activities of daily living (ADL) across three domains (mobility, self-care, and caregiver-assistance), as assessed by the Mucopolysaccharidosis Health Assessment Questionnaire (MPS-HAQ) after 72 and 120 weeks or approximately 1 and 2 years.

Results: Mean baseline MPS-HAQ domain scores showed impairments in mobility, self-care, and independence. The MOR-005 intent-to-treat population (ITT; N = 169, including 158 with 2 years follow-up) showed sustained significant reductions (representing improvements) in mobility and self-care domain least square (LS) mean scores vs. baseline at 1 and 2 years and a non-significant decrease in the caregiver-assistance domain at 2 years. At week 120, LS mean (SE) changes from baseline were − 0.5 (0.1) for mobility (P = 0.002), − 0.4 (0.1) for self-care (P = 0.001), and − 1.0 (0.5) for caregiver-assistance (P = 0.06) (ITT population). Improvements in MPS-HAQ domain scores vs. baseline at 1 and 2 years were greater in patients continuously treated with the weekly dosing regimen than in the total MOR-005 population and statistically significant across domains. A comparable untreated cohort of patients from the Morquio A Clinical Assessment Program (MorCAP) natural history study (ITT population, N = 94, including 37 with 2 years follow-up) showed no improvement over 2 years, with two of the three domains worsening (LS mean (SE) changes from baseline: 0.3 (0.3) for mobility, 0.4 (0.2) for self-care, − 0.5 (0.8) for caregiver-assistance). Changes in LS mean scores vs. baseline were statistically significantly different between MOR-005 and MorCAP for the mobility domain (− 0.7 (SE 0.4), P = 0.0490) and the self-care domain (− 0.7 (SE 0.3), P = 0.0146) at 2 years.

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https://doi.org/10.1016/j.ymgme.2017.11.015
Received 27 October 2017; Received in revised form 30 November 2017; Accepted 30 November 2017
Available online 05 December 2017

Conclusions: Together, these findings suggest that long-term elosulfase alfa ERT is associated with partial recovery of functional abilities, improving Morquio A patients' abilities to perform ADL.

Trial registration: ClinicalTrials.gov NCT01415427. Registered 8 August 2011, retrospectively registered.

1. Background

Morquio A syndrome, also called mucopolysaccharidosis (MPS) IVA, is an inheritable progressive disease caused by a deficiency of the lysosomal enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS) [1,2]. Lack of GALNS activity leads to widespread accumulation of keratan sulfate (KS) in tissues and organs, causing progressively worsening clinical manifestations and early mortality [2–4]. Characteristic musculoskeletal manifestations of Morquio A include short-trunk dwarfism, short neck, dysostosis multiplex, and joint abnormalities [5]. Patients also frequently develop dysfunctions in the respiratory, cardiac, neurological, and gastrointestinal systems, and impaired vision and hearing [6]. There is great variation between Morquio A patients in terms of clinical manifestations, disease severity, progression rate, and life expectancy [6].

The clinical manifestations of Morquio A can considerably affect endurance, mobility, and self-care, which in turn increase the need for assistance from caregivers, usually provided by the patient's parents [7,8]. Endurance and/or mobility can be impaired due to skeletal and joint abnormalities, pain in the hips and lower limbs (knee valgus, ankle valgus), cardiorespiratory disease, and neurological problems secondary to spinal cord compression. Factors that may affect self-care include impaired mobility, short stature, joint deformities and laxity in the upper limbs (mainly in wrists, fingers, and elbows), poor shoulder range of motion, neurological disease, and impaired vision and hearing [7]. In the International Morquio A registry, including 326 Morquio A patients, only 40–60% of patients (depending on the activity assessed) were able to independently perform activities of daily living (ADL) such as taking a bath, putting on clothes, taking off clothes, riding a bicycle, or swimming [9]. The Morquio A Clinical Assessment Program (MorCAP, #NCT00787995) natural history study (N = 325), demonstrated an impact of the disease on self-care activities (dressing, eating, drinking, bathing, tooth brushing, toileting) in around 20–40% of patients (depending on the activity assessed) [5].

Elosulfase alfa (recombinant human GALNS, BioMarin Pharmaceutical Inc.) enzyme replacement therapy (ERT) is an approved, systemic, pharmaceutical treatment for Morquio A. In the pivotal multi-center, randomized, double-blind, placebo-controlled, phase 3 trial (MOR-004, #NTC01275066; N = 176), patients treated with elosulfase alfa 2.0 mg/kg/week for 24 weeks showed a significant increase in the distance walked in the 6-min walk test (6MWT) [10], a rapid and sustained reduction in urine KS, and numerical improvements vs. placebo in several secondary and tertiary endpoints, including respiratory function. Long-term follow-up in the MOR-005 extension of the phase 3 trial (#NCT01415427) demonstrated sustained improvements from baseline in endurance and respiratory function over 2 years, as compared to sustained worsening in these outcomes in corresponding untreated patients from the MorCAP natural history study [11,12]. ADL were also assessed as a tertiary efficacy endpoint of MOR-004 across three domains (mobility, self-care, and caregiver-assistance), using the MPS Health Assessment Questionnaire (MPS-HAQ) [10]. After 24 weeks, numerical improvements vs. placebo were seen in the caregiver-assistance and mobility domain scores, though with wide confidence intervals [13]. The proportion of patients improving from baseline during this period was higher for patients treated with elosulfase alfa 2.0 mg/kg/week for 34 of the 52 items of the MPS-HAQ, higher for the placebo group for 12 items, and similar in both groups for 6 items [13]. Here, we report the long-term impact of elosulfase alfa on ADL in the MOR-005 extension study.

2. Material and methods

2.1. Study objectives

The aim of this study was to present MPS-HAQ outcomes over 1 and 2 years in the MOR-004/005 trial and to compare these with MPS-HAQ outcomes over a similar time period in a comparable untreated cohort of Morquio A patients from the MorCAP natural history study.

2.2. Study design

MOR-005 is a multi-national, multi-center, open-label, extension of the 24-week randomized, double-blind, placebo-controlled, phase 3 trial (MOR-004). MOR-004 included 176 Morquio A patients ≥ 5 years of age with 6MWT distances ≥ 30 and ≤ 325 m at baseline [10]. All patients completing the pivotal study were eligible for enrollment in MOR-005. The study designs of MOR-004 and MOR-005 have been discussed in previous publications [10,11]. During part 1 of the MOR-005 study, patients initially randomized to elosulfase alfa in MOR-004 remained on their assigned dosing regimen of 2.0 mg/kg/week (QW) or every other week (QOW). Placebo-treated patients were re-randomized (1:1) to one of these dosing regimens. Part 2 started when all patients were switched to the weekly dosing regimen, which was established as the recommended dose after review of the final results of MOR-004. Timing of transition to weekly dosing was at a specific date and ranged from week 36 to week 96, depending on the time of study enrolment. Planned major surgical procedures, although prohibited during MOR-004, were allowed during MOR-005.

All procedures followed were in accordance with the ethical standards of the responsible local ethics committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Each participant, or his/her legally authorized representative, provided written informed consent before entering the study in compliance with the applicable local regulations.

2.3. Evaluation of ADL

ADL were assessed using the MPS-HAQ. The MPS-HAQ is a questionnaire based on the Health Assessment Questionnaire (HAQ), originally developed for patients with rheumatoid arthritis [14], and is used in studies in MPS I, MPS II, and MPS VI that involve skeletal abnormalities [5,9,10,15–17]. It 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 (Supplementary file 1). The domain score for self-care was calculated as the sum of scores from questions 1 to 27 divided by 27 minus the number of missed questions. The mobility domain score was calculated as the sum of scores from questions 28 to 39, excluding questions 33 and 34 (which were rated differently than the other mobility questions), divided by 10 minus the number of missed questions. The excluded questions ask about use of wheelchairs and walking aids specifically. Total self-care and mobility domain scores range from 0 (not difficult at all) to 10 (extremely difficult) and 11 (unable to do). The caregiver-assistance domain score was calculated as the sum of responses to questions 40 through 52 (which were each rated 1 to 4, with 1 = independence, 2 = minimal assistance required, 3 = moderate assistance required, 4 = complete assistance required); total domain score ranges from 13 (independent) to 52 (complete assistance required).

2.4. Statistical methods

Data were collected during the 24-week MOR-004 study and 96 weeks of the MOR-005 extension study, representing a total of up to 120 weeks of ERT (96 weeks for the patients originally included in the placebo group). Results are reported for the intent-to-treat (ITT) population, including all patients who were previously included in MOR-004 and had received at least one dose of elosulfase alfa in MOR-005, and a modified per-protocol (MPP) population. The MPP is a subset of the ITT population that excludes patients who had orthopedic surgery during the study or were non-compliant with study protocol (missed ≥ 20% of scheduled infusions). Further details have been described previously [11]. Descriptive statistics of MPS-HAQ results are provided for both populations.

The variable timing of transition to weekly dosing and the small sample sizes of the two treatment groups originally randomized to placebo precluded comparison of dosing regimens. Therefore, data from all treatment groups, including patients consistently treated with the weekly dosing regimen as well as those originally receiving every other week dosing, were combined for the analysis. Results are also presented separately for the cohort of patients continuously receiving the recommended weekly dosing regimen (QW-QW).

A repeated measures analysis of covariance (ANCOVA) model was used to calculate least square (LS) mean changes from MOR-004 baseline for MOR-005 ITT and MorCAP populations. MorCAP patients included in the analysis were ≥ 5 years old, and had a baseline 6MWT distance ≥ 30 and ≤ 325 m and 1 and/or 2-year follow-up data available. MOR-005 weeks 72 and 120 were considered year 1 and 2, respectively. The model included treatment, time point, treatment and time point interaction, and baseline measurement.

3. Results

3.1. Baseline demographics and patient characteristics

Baseline (MOR-004) demographics and patient characteristics of MOR-005 patients included in the analysis were comparable to those of the untreated patients from MorCAP used for comparison of MPS-HAQ results, although the MOR-005 population included more non-white patients and the MorCAP population contained a higher percentage of female patients (Table 1). In addition, the mean age of MorCAP patients was higher, but median age was similar between groups.

Mean baseline MPS-HAQ domain scores showed impairments in mobility, self-care, and independence (Table 2 and Supplementary file 2). In the MOR-005 ITT population, mean caregiver-assistance domain score was 27.4 on a 13 (independent) to 52 (complete assistance required) scale, mean mobility and self-care scores were 4.8 and 3.7, respectively, on a 0 (without difficulty) to 11 (unable to do) scale. The greatest impairment in the caregiver-assistance domain was seen for car transfers and dressing lower body (mean score ≥ 2.5); in the mobility and self-care domains, the greatest impairments were seen for opening/closing car doors, walking supermarket aisles, walking across uneven surfaces, stepping on/off curbs, opening jars, tucking in shirts, cutting fingernails with clippers, and tying shoelaces (mean scores ≥ 5).

Baseline MPS-HAQ domain scores in MOR-005 and MorCAP patients were comparable, with the exception of the mean self-care domain score, which was slightly worse in the MOR-005 population (Table 2). The number of patients with 2-year follow-up from MorCAP was substantially smaller than the number at baseline, but the baseline characteristics of the MOR-005 and MorCAP patients contributing to the year 2 analysis remained similar, although MorCAP patients were slightly older and taller (Supplementary file 3).

3.2. Change over 2 years in MPS-HAQ scores in MOR-005 patients vs. untreated natural history controls

MOR-005 patients showed sustained significant reductions (representing improvements) in mobility and self-care domain LS mean scores vs. baseline at 1 and 2 years and a trend toward a decrease in the level of caregiver-assistance required at 2 years (Fig. 1 and Table 2). Items showing improvement (reduction ≥ 1 point) in individual MPS-HAQ items most frequently are shown in Fig. 2. Patients with a baseline caregiver-assistance score above the mean score of 27.3 (N = 77) showed significant improvements at 1 year (− 3.2; $P = 0.0002$) and at 2 years (− 4.0; $P < 0.0001$); patients with a baseline score below the mean score (N = 92) showed no significant improvements at 1 and 2 years, suggesting a ceiling effect. When patients who underwent orthopedic surgeries or missed ≥ 20% of their scheduled infusions were excluded (MPP population), mobility and self-care domain results were similar to the ITT results and the level of caregiver-assistance required decreased significantly at 2 years. Although the mobility domain score indicated an improvement in mobility, the percentage of patients using wheelchairs (based on question 33) increased slightly over the course of the study (from 49.7% to 57.6%).

Table 1
Baseline (MOR-004) demographics and patient characteristics.

	MOR-005 ITT	MOR-005 ITT QW-QW	MorCAP All	MOR-005 MPP	MOR-005 MPP QW-QW	MorCAP excluding patients with major surgeries[b]
	N = 169[a]	N = 55	N = 94	N = 124[a]	N = 43	N = 78
Age, years						
Mean (SD)	14.4 (10.3)	12.7 (8.1)	17.0 (12.4)	15.4 (10.3)	13.5 (8.6)	18.4 (13.1)
Median	11.7	10.0	11.9	15.4	11.1	12.3
Min-max	5.0–57.4	5.0–41.9	5.0–65.6	5.0–49.1	5.0–41.9	5.0–65.6
Gender, n (%)						
Male	85 (50.3%)	26 (47.3%)	40 (42.6%)	66 (53.2%)	21 (48.8%)	31 (39.7%)
Female	84 (49.7%)	29 (52.7%)	54 (57.4%)	58 (46.8%)	22 (51.2%)	47 (60.3%)
Height, cm						
Mean (SD)	103.9 (15.4)	101.5 (13.2)	106.4 (14.2)	105.3 (16.3)	103.2 (13.9)	106.2 (14.3)
Median	99.6	98.7	102.0	105.3	99.6	106.2
Min-max	81.0–165.0	82.7–141.4	83.0–150.5	81.0–165.0	84.7–141.4	83.0–150.5
Weight, kg						
Mean (SD)	24.9 (11.5)	22.8 (10.7)	26.1 (10.4)	26.5 (12.4)	24.2 (11.6)	26.5 (10.5)
Median	21.8	18.0	23.9	26.5	19.6	26.5
Min-max	11.4–68.5	12.0–68.5	12.2–67.0	11.4–68.5	12.0–68.5	12.5–67.0

Data from the MOR-005 intent-to-treat (ITT) and modified per-protocol (MPP) population and comparable untreated patients from the MorCAP natural history study.
[a] Height and weight data from 168 patients in the ITT and 123 in the MPP population.
[b] MorCAP cohort comparable to the MOR-005 MPP population.

Table 2
ANCOVA model of MPS Health Assessment Questionnaire (MPS-HAQ) domain scores in MOR-005 and MorCAP.

	Baseline			Year 1			Year 2		
	MOR-005	MOR-005 QW-QW	MorCAP	MOR-005	MOR-005 QW-QW	MorCAP	MOR-005	MOR-005 QW-QW	MorCAP
ITT									
Caregiver-assistance domain									
N	169	55	93[a]	168	55	79	158	53	36
LS mean (SE)	27.4 (0.4)	27.6 (0.8)	27.3 (0.4)	26.6 (0.4)	25.8 (0.8)	26.8 (0.5)	26.4 (0.4)	25.7 (0.8)	26.8 (0.7)
LS mean change from baseline (SE)				− 0.8 (0.5)	− 1.8 (1.0)	− 0.5 (0.6)	− 1.0 (0.5)	− 1.9 (1.0)	− 0.5 (0.8)
P-value				0.1282	0.0676	0.4067	0.0625	0.0617	0.5123
Mobility domain									
N	169	55	94	168	55	79	158	53	37
LS mean (SE)	4.8 (0.1)	4.6 (0.2)	4.8 (0.2)	4.2 (0.1)	3.9 (0.2)	4.3 (0.2)	4.3 (0.1)	4.0 (0.2)	5.1 (0.3)
LS mean change from baseline (SE)				− 0.6 (0.1)	− 0.7 (0.2)	− 0.5 (0.2)	− 0.5 (0.1)	− 0.6 (0.2)	0.3 (0.3)
P-value				**< 0.0001**	**0.0061**	**0.0216**	**0.0016**	**0.0161**	0.3782
Self-care domain									
N	169	55	94	168	55	79	158	53	37
LS mean (SE)	3.7 (0.1)	3.8 (0.2)	3.2 (0.1)	3.4 (0.1)	3.3 (0.2)	3.0 (0.1)	3.3 (0.1)	3.1 (0.2)	3.6 (0.2)
LS mean change from baseline (SE)				− 0.3 (0.1)	− 0.5 (0.2)	− 0.2 (0.2)	− 0.4 (0.1)	− 0.7 (0.2)	0.4 (0.2)
P-value				**0.0127**	**0.0190**	0.2291	**0.0011**	**0.0018**	0.1024
MPP									
Caregiver-assistance domain									
N	124	43	77	124	43	67	122	43	25
LS mean (SE)	26.3 (0.5)	26.3 (0.9)	26.4 (0.5)	25.5 (0.5)	23.7 (0.9)	25.7 (0.5)	25.0 (0.5)	24.0 (0.9)	26.1 (0.8)
LS mean change from baseline (SE)				− 0.8 (0.6)	− 2.6 (1.1)	− 0.7 (0.6)	− 1.3 (0.6)	− 2.3 (1.1)	− 0.3 (0.9)
P-value				0.1917	**0.0209**	0.2727	**0.0288**	**0.0387**	0.7734
Mobility domain									
N	124	43	78	124	43	67	122	43	26
LS mean (SE)	4.7 (0.1)	4.2 (0.2)	4.7 (0.2)	4.0 (0.1)	3.4 (0.2)	4.3 (0.2)	4.0 (0.1)	3.5 (0.2)	4.9 (0.3)
LS mean change from baseline (SE)				− 0.7 (0.2)	− 0.8 (0.3)	− 0.5 (0.2)	− 0.6 (0.2)	− 0.7 (0.3)	0.1 (0.3)
P-value				**< 0.0001**	**0.0018**	**0.0469**	**< 0.0001**	**0.0111**	0.6861
Self-care domain									
N	124	43	78	124	43	67	122	43	26
LS mean (SE)	3.3 (0.1)	3.5 (0.2)	3.0 (0.1)	3.0 (0.1)	2.8 (0.2)	3.0 (0.1)	2.9 (0.1)	2.6 (0.2)	3.2 (0.2)
LS mean change from baseline (SE)				− 0.3 (0.1)	− 0.7 (0.2)	− 0.0 (0.2)	− 0.4 (0.1)	− 0.8 (0.2)	0.2 (0.2)
P-value				**0.0235**	**0.0009**	0.9140	**0.0036**	**< 0.0001**	0.3840

LS mean domain scores and LS mean changes from baseline at 1 and 2 years in the MOR-005 intent-to-treat (ITT) and modified per-protocol (MPP) populations, patients from the ITT and MPP populations continuously treated with the weekly dose of elosulfase alfa (MOR-005 QW-QW), and in untreated comparable patients from the MorCAP natural history study.
P-values represent changes from baseline to year 1 and year 2 (*P*-values ≤ 0.05 are indicated in bold).
Year 1 and year 2 correspond with 72 and 120 weeks, respectively.
[a] One caregiver-assistance score is missing as too many items contributing to this score were not completed.

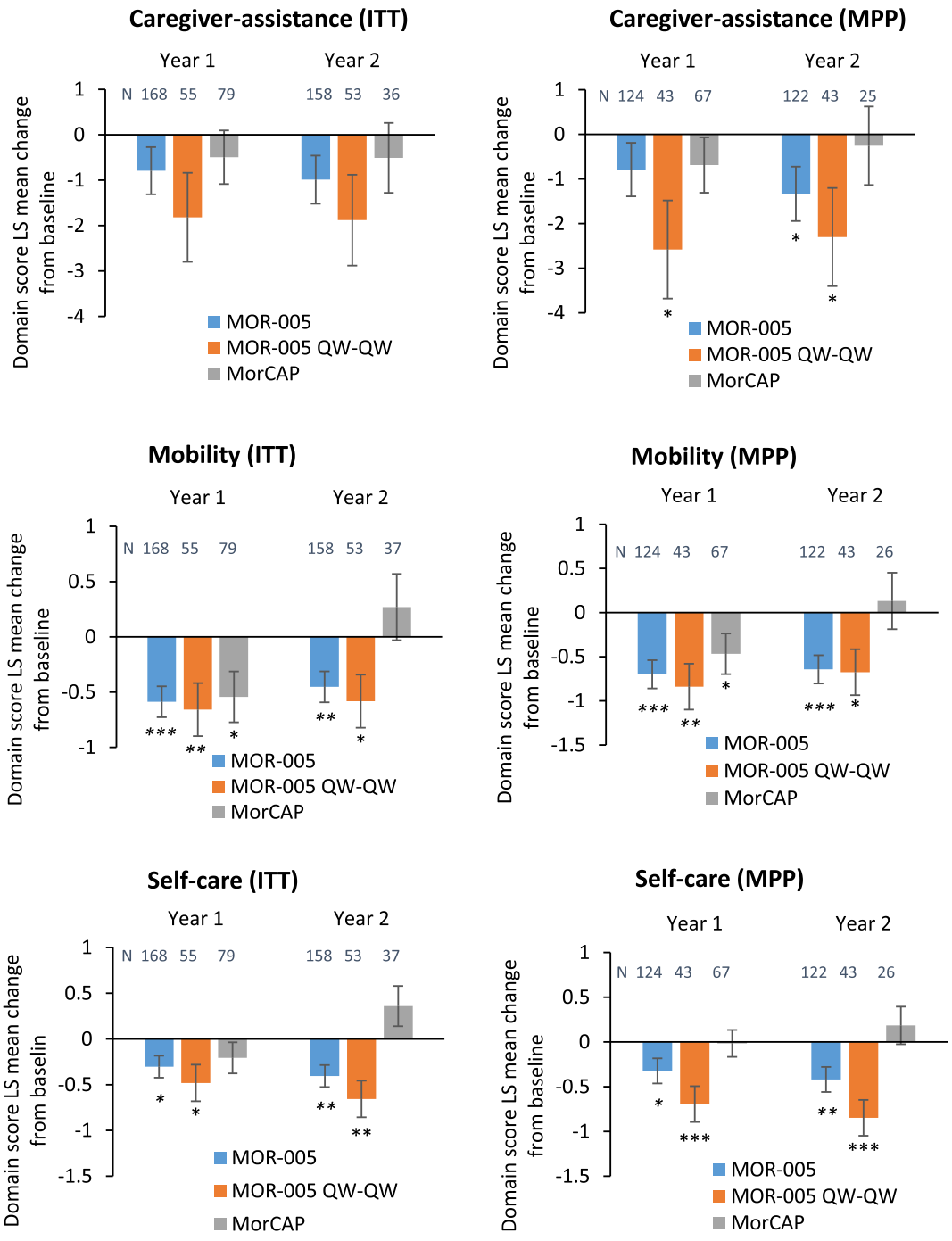

Fig. 1. ANCOVA model of MPS Health Assessment Questionnaire (MPS-HAQ) domain scores.
LS mean changes from baseline at 1 and 2 years in the MOR-005 intent-to-treat (ITT) and modified per-protocol (MPP) population, patients from the ITT and MPP population continuously treated with the weekly dose of elosulfase alfa (MOR-005 QW-QW), and comparable untreated patients from the MorCAP natural history study. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. baseline; error bars represent standard errors. Year 1 and year 2 correspond with MOR-005 week 72 and 120, respectively.

Improvements in caregiver-assistance, mobility, and self-care domains vs. baseline at 1 and 2 years were greater in patients continuously treated with the weekly dosing regimen (N = 55) than in the total MOR-005 population and statistically significant across all domains (Fig. 1 and Table 2). None of the other treatment arms showed consistently significant improvements over 2 years for both the ITT and MPP population in any of the MPS-HAQ domains, although patient numbers in the placebo-switch groups were too low to allow firm conclusions.

Comparable untreated MorCAP patients showed no improvement over 2 years, with two of the three domains (mobility and self-care) worsening (Fig. 1 and Table 2). There was an initial significant improvement in the LS mean mobility domain score vs. baseline (at 1 year), though less pronounced than in MOR-005 patients; but this was not sustained at 2 years. Changes in LS mean scores vs. baseline were statistically significantly different between MOR-005 and MorCAP for the mobility domain (− 0.7 (SE 0.4), $P = 0.0490$) and the self-care domain (− 0.7 (SE 0.3), $P = 0.0146$) at 2 years (ITT population). Despite the improvement from baseline in the MOR-005 population, no significant differences between MOR-005 and MorCAP were seen in the caregiver-assistance domain.

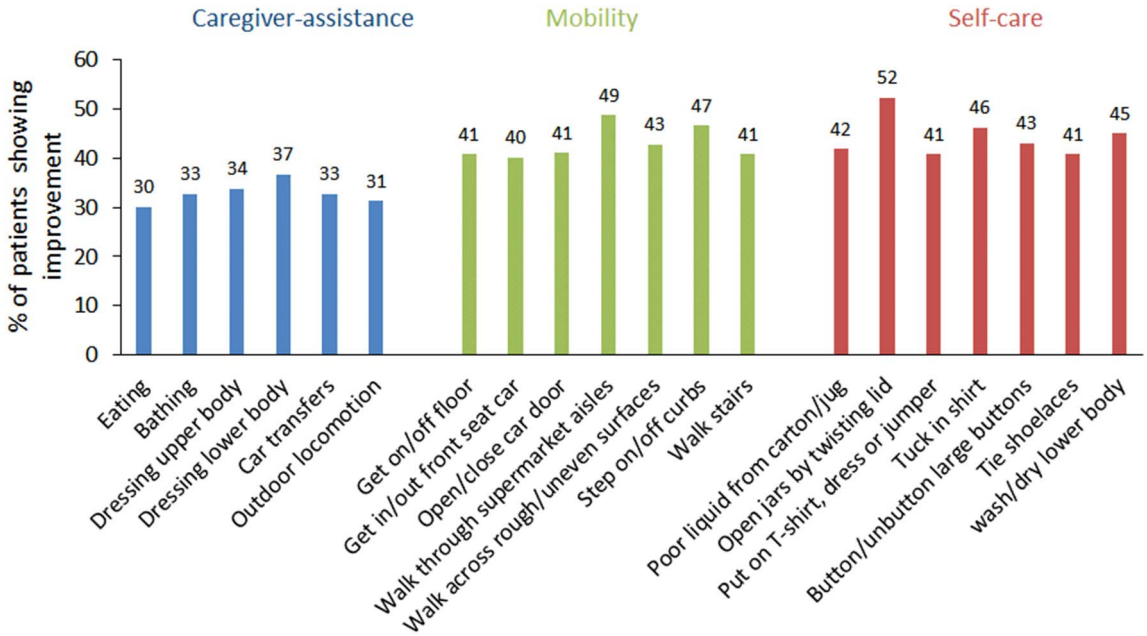

Fig. 2. Percentage of patients showing improvement in individual MPS-HAQ items.
Improvement was defined as a decrease of ≥ 1 point on a 1 (independence) to 4 (complete assistance required) scale for the caregiver-assistance domain items and on a 0 (without difficulty) to 11 (unable to do) scale for the mobility and self-care domain items. Caregiver-assistance domain items showing improvement in ≥ 30% of patients and mobility and self-care domain items showing improvement in ≥ 40% of patients are shown.

4. Discussion

Morquio A syndrome is a very debilitating disorder, associated with progressively worsening skeletal and non-skeletal manifestations and a gradual decline in endurance/mobility and respiratory function over time [9,18]. Studies using patient-reported outcomes have provided important insight into how Morquio A affects the lives of patients and their caregivers on a daily basis. MPS-HAQ data from the International Morquio A Registry (N = 326) and the MorCAP natural history study (N = 325) demonstrated considerable limitations in the ability of patients to perform ADL independently [5,9]. The most important impairments in ADL reported in the MorCAP study (scored unable to do/complete assistance required) included fingernail clipping (41%), tying shoelaces (31%), tucking in shirts (22%), opening jars (19%), zipping/unzipping (16%), and brushing hair, washing, and pouring liquid (all 16%) [5]. The Morquio A patient-reported outcomes (PRO) study, including 36 children and 27 adults with Morquio A, showed decreasing mobility (increasing wheelchair use) and an increasing need for caregiver-assistance with ageing [7,8]. Overall, the baseline MPS-HAQ results of the MOR-005 study confirm these findings.

Patients receiving ERT in MOR-005 showed sustained improvements in all domains of the MPS-HAQ (mobility, self-care, and caregiver-assistance) over 2 years, with the greatest improvements seen in the mobility domain. Patients receiving the recommended weekly dosing regimen of elosulfase alfa throughout the study had greater improvements across all domains than the total MOR-005 population, confirming the appropriateness of this dosing regimen. Interestingly, although the mobility domain score indicated a significant improvement over 2 years in mobility in the MOR-005 population, the percentage of patients using wheelchairs increased slightly over the course of the study. This apparent contradiction may be caused by decreasing fatigue resulting in a more active lifestyle, which may require the use of a wheelchair to accommodate a wider range of activities.

ERT-treated patients from the MOR-005 study had significantly better MPS-HAQ outcomes than a cohort of comparable untreated Morquio A patients from the MorCAP natural history study. These untreated patients showed no improvement over 2 years, with two of three domains (mobility and self-care) worsening, as would be expected in this progressive disease. Part of the initial improvements in the mobility and self-care domains, as well as the small improvement over 2 years in the caregiver-assistance domain, may be due to the fact that most patients were children, with the youngest being only 5 years old at baseline. In these young patients, ageing may have led to better abilities to perform some of the activities listed in the MPS-HAQ, particularly in domains where children are more dependent on their parents. The same applies to the MOR-005 population. However, although the mean age of MOR-005 patients contributing to the 2-year analysis was slightly below that of the MorCAP patients in this analysis, it is unlikely that the ageing effect explains the significant differences between both populations, favoring ERT-treated patients, after 2 years. The favorable effect of ERT is further supported by the evidence that patients continuously treated with the weekly dose of elosulfase alfa, since the beginning of the MOR-004 study, show the greatest improvements in all domains. As the mean age of the patients in this group was slightly below that of the whole MOR-005 population, ageing might also have contributed to this result.

The improvements in ADL seen with elosulfase alfa might be (partly) related to the previously reported sustained improvements in endurance and respiratory function over 2 years in the MOR-005 population (vs. a sustained decline in untreated MorCAP patients) [11,12]. The mechanism underlying improvements in respiratory function remains to be established, but is likely multifactorial, including growth acceleration (in younger patients), decreased upper airway obstruction, increased chest wall compliance, improved respiratory muscle strength, and/or improved diaphragmatic movement due reduced liver size and declined GAG tissue storage. Mechanisms possibly underlying improvements in endurance include improved cardiorespiratory function, and improved muscle strength, joint movement, and pain/fatigue in the lower limbs. Improvements in muscle strength, joint movement, and/or pain/fatigue in the upper limbs may also have contributed to the effect of ERT on ADL [19]. In the phase 2 MOR-008 study, Morquio A patients (N = 25), aged ≥ 7 years and able to walk ≥ 200 m in the 6MWT, showed numerical improvements in muscle strength (knee extension, and elbow and knee flexion) and reduction of pain after 25 weeks of ERT [19]. The study also showed improvements in exercise capacity and efficiency of

oxygen utilization, not attributable to changes in cardiac or pulmonary function [20]. The long-term impact of ERT on muscle strength and pain needs to be established. In addition, the long-term impact of ERT on bone disease has not been addressed in this and previous reports, and requires further study.

Impaired physical functioning can have a direct impact on the quality of life (QoL) of patients and their caregivers. In the previously mentioned Morquio A PRO study (N = 63), patients showed reduced health-related QoL in the EuroQoL (EQ)-5D-5L questionnaire, mostly driven by poor scores in the mobility, self-care, and usual activities domains [7]. The patients' caregivers experienced a negative impact of Morquio A on their family, social life, physical and emotional health, and family income [8]. The need for assistance with ADL and the burden on caregivers increased with disease progression [8]. The latter can also produce a considerable burden (cost) for society. Previous research has shown correlations between endurance/mobility (6MWT and 3-minute stair climb test) and respiratory function (maximum voluntary ventilation) outcomes with health-related QoL in the EQ-5D-5L in Morquio A patients [21]. Although the correlation between MPS-HAQ scores and QoL needs to be established, it can logically be anticipated that maintenance or improvement of functional capacity and mobility will help to support a better QoL.

The MOR-005 study and the comparison with patients from the MorCAP study are subject to some limitations, which have been discussed in detail in the primary MOR-005 publication [11]. Briefly, the variability in timing of transition to elosulfase alfa weekly dosing of those originally receiving the QOW dosing regimen in MOR-005 (ranging from week 36 to 96) may have biased the analysis in favor of finding no effect of treatment because not all patients were receiving the optimal dose for the full study. Limitations of the comparison of MOR-005 patients with patients from the MorCAP study include the decreasing number of observations, potential differences that may exist between the MorCAP and MOR-005 populations and test executions, and the fact that some patients contribute to both populations (29 patients from the ITT population and 21 from the MPP population at baseline; 10 and 4 patients, respectively, at year 2) [11]. In addition, it cannot be ruled out that part of the difference between the results in the MorCAP and elosulfase alfa clinical trial populations could be explained by a positive impact of increased frequency of clinical visits.

5. Conclusions

The present analysis confirms results from previous studies showing a negative impact of Morquio A syndrome on the patients' ability to perform ADL. The long-term follow-up data of MOR-005 suggest that elosulfase alfa ERT has the potential to slow down, and even partially reverse, the natural deterioration in functional capacity associated with Morquio A syndrome for at least 2 years. The mechanism underlying this effect of ERT warrants further study, but is likely multifactorial and comprised of improvements in endurance, respiratory function, muscle strength, joint movement, pain, and/or fatigue.

Competing interests

CJH declares receipt of consulting fees from Actelion, Amicus, Alexion, BioMarin, Inventiva, Sanofi Genzyme, Shire, Chiesi, and Integrated therapeutic solutions, contracted research for Sanofi Genzyme, Shire, and Actelion, and ownership interest in FYMCA Medical Ltd. over the past 12 months. RP declares board membership for BioMarin and payments for lectures and travel/accommodation/meeting expenses from BioMarin, Shire, and Sanofi Genzyme. MDA declares payments for lectures and travel/accommodation/meeting expenses from BioMarin. JR declares board membership for Shire and BioMarin and payments for lectures and travel/accommodation/meeting expenses from BioMarin, Shire, Genzyme, and Actelion. RG declares board membership for Amicus, Sanofi-Genzyme, Shire, Armagen, Green Cross, and BioMarin, consultancy for Genzyme, Shire, and BioMarin, grants from Genzyme, Shire, BioMarin, Actelion, Alexion, Ultragenyx, and Amicus, payments for lectures from Actelion, Genzyme, Shire, BioMarin, Actelion, Alexion, and PTC, and payments for travel/accommodation/meeting expenses from Genzyme, Shire, BioMarin, Amicus, and Actelion. JJM declares consultancy for BioMarin, Shire, and Genzyme, grants from BioMarin and Shire, and payments for lectures form BioMarin. BKB declares consultancy for BioMarin, Shire, Alexion, Sanofi Genzyme, ReGenX Bio, Armagen, and Retrophin, grants (including clinical trial funding) from Shire, BioMarin, Alexion, Ultragenyx, and Armagen, payments for lectures from Shire and Alexion, and payments for travel/accommodation/meeting expenses from Shire, BioMarin, Sanofi Genzyme, Alexion, and Retrophin. NG received speaker's fees and travel support from BioMarin. FJS declares speaker fees from Genzyme and consultancy and payments for lectures and travel/accommodation/meeting expenses from BioMarin. DAH declares consultancy for BioMarin. RM, SMH and CD are employees and stock holders of BioMarin Pharmaceutical Inc. PRH declares board membership for BioMarin, and PTC, consultancy for BioMarin, Shire, Genzyme, PTC, Chiesi, Armagen, Inventiva, REGENXBIO, Sangamo, and Alexion, grants from BioMarin, payments for lectures from BioMarin, Shire, Genzyme, Alexion, and PTC, and payments for travel/accommodation/meeting expenses from BioMarin, Genzyme, Chiesi, and Armagen.

Funding

This study and support in the process of manuscript development were funded by BioMarin Pharmaceutical Inc. The site in Monza (Dr. Parini) received continuous economical support for the clinical work of the Center from Fondazione Pierfranco and Luisa Mariani. Dr. Mitchell receives research support from Dr. Eleanor Mackenzie Harpur Pediatric Endowment Fund. This publication was supported in part (Dr. Harmatz) by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through UCSF-CTSI Grant Number UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2017.11.015.

Acknowledgements

The authors are grateful to Ismar Healthcare NV (Lier, Belgium) for their assistance in the writing of the manuscript, which was funded by BioMarin Pharmaceutical Inc. The site in Monza (Dr. Parini) wants to acknowledge Fondazione Pierfranco and Luisa Mariani for their continuous economical support to the clinical work of the Center. This publication was supported in part (Dr. Harmatz) by the National Center for Advancing Translational Sciences, NIH, through UCSF-CTSI Grant Number UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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