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Longitudinal analysis of endurance and respiratory function from a natural history study of Morquio A syndrome

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ABSTRACT

Objectives: Baseline data from the Morquio A Clinical Assessment Program (MorCAP) revealed that individuals with Morquio A syndrome show substantial impairment in multiple domains including endurance and respiratory function (Harmatz et al., *Mol Genet Metab*, 2013). Here, 1- and 2-year longitudinal endurance and respiratory function data are presented.

Methods: Endurance was assessed using the 6-minute walk test (6MWT) and the 3-minute stair climb test (3MSCT). Respiratory function was evaluated by measuring forced vital capacity (FVC) and maximum voluntary ventilation (MVV). Data were analyzed using repeated measures ANCOVA models. Annualized estimates of change were determined using model estimates and interpolation.

Results: 353, 184, and 78 subjects were assessed at Year 0 (baseline), Year 1, and Year 2, respectively. The overall annualized estimate of change (SE) in 6MWT distance was -4.86 ± 3.25 m; a larger decline of -6.84 ± 5.38 m was observed in the subset of subjects meeting the inclusion/exclusion criteria of the Phase 3 clinical trial of elosulfase alfa (≥5 years of age with baseline 6MWT distance ≥30 and ≤325 m). In contrast, little change (-0.14 ± 0.60 stairs/min) was observed in 3MSCT. Annualized changes (SE) in FVC and MVV were 2.44 ± 0.68% and 1.01 ± 2.38%, respectively. FVC and MVV increased in patients aged ≤14 years, but decreased in older patients.

Conclusions: The natural history of Morquio A syndrome is characterized by progressive impairment of endurance as measured by the 6MWT. Longitudinal trends in FVC and MVV showing increase in younger patients, but decrease in older patients, are likely to be influenced by growth. Changes in 6MWT may represent a sensitive measure of disease progression in ambulatory Morquio A patients.

1. Introduction

Morquio A syndrome, or mucopolysaccharidosis IVA (MPS IVA), is a rare lysosomal storage disorder caused by deficient activity of N-acetyl-

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galactosamine-6-sulfatase (GALNS), an enzyme that degrades the glycosaminoglycans (GAG) keratan sulfate and chondroitin-6-sulfate. Intracellular GAG accumulation leads to the development of multisystemic impairments, including short stature, skeletal deformities, joint abnormalities, obstructive and restrictive respiratory disease, and cardiac valve disease [1–7]. Over 275 *GALNS* mutations have been identified, resulting in wide phenotypic heterogeneity [5,8–12]. Life expectancy is shortened, with survival often limited to the second or third decade in patients with "classical phenotype", but ranging up to and beyond 60 years in a few patients [1,4,5]. Death is commonly due to cardiorespiratory or neurological complications [1,4,13]. The management of Morquio A syndrome has until recently been limited to supportive and symptom-based care, but enzyme replacement therapy (ERT) with elosulfase alfa has now become available as a treatment option [14].

The natural history of Morquio A syndrome is currently not well defined. Characterization of the range and progression of symptoms across a large subject population is expected to lead to improved understanding and management of the disorder. The Morquio A International Registry has published information about the manifestations and natural course of Morquio A syndrome based on self-reported questionnaires obtained from 326 patients [1]. However, clinical evaluations are required to better characterize the natural course of this condition. The Morquio A Clinical Assessment Program (MorCAP) is a multicenter, multinational, longitudinal natural history study designed to describe the spectrum and progression of symptoms in untreated Morquio A syndrome through direct clinical observation and assessments [2]. Baseline data collected from the first 325 patients enrolled in MorCAP demonstrated substantial impairment in multiple domains including endurance, mobility, respiratory function and growth [2]. Musculoskeletal manifestations, including short stature, abnormal gait, genu valgum and pectus carinatum, were reported in more than 90% of MorCAP patients and contribute to the observed functional limitations. Wheelchair and walk aid use were found to be common among MorCAP subjects.

Submaximal intensity endurance tests such as the 6-minute walk test (6MWT) assess cardiorespiratory and musculoskeletal function and are recognized as clinically meaningful outcome measures in MPS disorders [15–19]. The 6MWT was used as the primary measure of efficacy in the Phase 3 randomized, double-blind, placebo-controlled clinical trial of elosulfase alfa, in which a statistically significant improvement of 22.5 m in 6MWT distance over placebo was demonstrated at 24 weeks [20]. The 3-minute stair climb test (3MSCT) was a secondary endpoint in this study but did not show statistically significant improvement with treatment [20]. In addition to endurance measures, respiratory function tests have also been included as efficacy endpoints in ERT studies for MPS disorders including Morquio A syndrome [16,17,20,21]. MorCAP baseline data revealed severe limitations in walking and stair climbing ability among subjects, with mean 6MWT distance of 212.6 ± 152.2 m and mean 3MSCT of 30.0 ± 24.0 steps/min [2]. Respiratory function was also severely compromised in the MorCAP population, with mean forced vital capacity (FVC) of 1.2 ± 0.9 L and mean maximum voluntary ventilation (MVV) of 34.8 ± 25.5 L/min [2]. This present study reports the functional endurance and respiratory function data obtained from MorCAP subjects who were followed for a minimum of 1 year and who completed assessments at the 1 year and/or 2 year follow-up visit(s).

2. Methods

2.1. Patients

MorCAP is a multicenter, multinational, observational study of individuals with Morquio A syndrome. Eligibility criteria for participation in MorCAP were described previously [2]. Briefly, individuals with documented reduced GALNS enzyme activity (relative to the normal range of the laboratory performing the assay) or genetic testing confirming a diagnosis of Morquio A syndrome were eligible. Individuals with a previous hematopoietic stem cell transplant (HSCT) or with a concurrent disease or condition that would interfere with study participation or pose a safety concern were excluded. The study was approved by all institutional review boards and ethics committees. Subjects gave written informed consent, or, in the case of subjects aged <18 years, written consent was obtained from a legally authorized representative. Subjects were free to enroll in ERT or other clinical trials but were no longer eligible to continue participation in the MorCAP study once this occurred.

2.2. Assessments

The 6MWT [22] and 3MSCT [23] were performed according to published guidelines. Respiratory function was evaluated based on measurements of forced expiratory time (FET), forced expiratory volume for 1 s (FEV_1), forced inspiratory vital capacity (FIVC), FVC, and MVV. These tests were conducted in accordance with the American Thoracic Society standards [24]. In the present study, FVC and MVV were selected as the most relevant respiratory function assessments for analysis; FVC is indicative of the degree of restrictive lung disease while MVV is a measure of airway resistance and respiratory muscle strength. Sites were provided with scheduling recommendations to ensure that patients received adequate rest between effort-based procedures. The study was initiated as a cross sectional study with only one visit per subject. The study was later amended to capture longitudinal data and this present analysis includes data from visits at baseline (Year 0), Year 1 and Year 2. Since subjects enrolled at variable calendar time and the amendment was initiated at a fixed time, the timing between visits at baseline and Year 1 varied by subject.

2.3. Statistical analysis

Baseline demographics and characteristics were summarized for all subjects who completed the Year 1 visit assessments and for subjects who completed the Year 2 visit assessments. Similar summaries were applied to the subset of subjects meeting the inclusion/exclusion criteria of the Phase 3 clinical trial of elosulfase alfa, i.e. ≥5 years of age at baseline with a baseline 6MWT distance ≥30 and ≤325 m [20], in order to assess disease progression in subjects similar to those undergoing experimental ERT. Limits for baseline 6MWT distance were applied to subjects in the pivotal Phase 3 study to evaluate those who were most likely to show improvement with treatment, i.e. the lower limit enabled exclusion of severely walk-impaired patients while the upper limit allowed exclusion of those subjects with walk distance approaching the normal range to avoid the potential for a ceiling effect [20].

The longitudinal data were summarized by visit. Because the timing between visits at baseline and Year 1 varied by subject, the windows were defined in order to capture the most data. The visit at baseline was defined as day 1; Year 1 visits included assessments collected between days 270 and 609 (approximately month 9 to 20, centered at day 439.5); Year 2 visits included assessments collected between days 610 and 944 (approximately month 21 to 31, centered at day 777).

Subjects who were physically unable to perform the functional endurance tests (6MWT and 3MSCT) had the functional tests scored as 0. Any other missing data were not imputed. Repeated measures ANCOVA models were used to estimate the change from baseline to Year 1 and Year 2 for 6MWT and 3MSCT and percent change from baseline to Year 1 and Year 2 for FVC and MVV assessments. For the analysis of change in 6MWT to Year 1 and Year 2, the model included analysis visit (Year 1 and Year 2), age group (0–4, 5–11, 12–18, ≥19 years), and baseline 6MWT category (0–<30, 30–≤200, >200–≤325, and >325 m) as factors, using unstructured variance. The analyses for 3MSCT, FVC and MVV used a similar model with the additional covariate

of the corresponding test's value at baseline. The mean follow-up time between baseline and Year 1 was 444 days, and between Year 1 and Year 2 was 352 days. Annualized estimates were obtained using the model estimates at Year 1 and Year 2 and interpolation. Changes in respiratory parameters were correlated with changes in endurance parameters.

3. Results

3.1. Patient characteristics

Baseline characteristics of the first 325 subjects enrolled in MorCAP have been published previously [2]. In the present study, baseline characteristics were summarized by duration of follow-up and the criteria of the Phase 3 clinical trial. Of the 353 subjects with data at baseline, 184 were followed to the Year 1 evaluation or later and 78 were followed to the Year 2 visit or later. Of the subset of patients who were ≥5 years of age with a baseline 6MWT distance of ≥30 and ≤325 m (the Phase 3-matched subjects), 97 were followed to Year 1 or later and 40 were followed to Year 2 or later. There were fewer observations at later visits due to a number of reasons:

- the later visits had not yet occurred for later accruals
- 123 subjects discontinued from MorCAP in order to enroll in ERT clinical trials
- subjects missed visits, or were discontinued for other reasons

Table 1 summarizes the baseline demographics and characteristics of the groups of subjects under evaluation. Baseline height, gender, endurance and respiratory function were similar across groups. The baseline mean age was slightly higher and the 6MWT ranges were narrower for the Phase 3-matched groups.

Table 1
Baseline demographics and characteristics of subjects.

	All subjects		Phase 3-matched subjects [a]	
	With Year 1 follow-up	With Year 2 follow-up	With Year 1 follow-up	With Year 2 follow-up
N	184	78	97	40
Female	100 (54.3%)	37 (47.4%)	56 (57.7%)	19 (47.5%)
Age at enrollment (years)				
n	184	78	97	40
Mean (SD)	14.4 (11.97)	15.4 (13.48)	16.3 (12.20)	17.0 (14.76)
Median	11.0	11.0	11.0	11.0
Min, max	1.0, 65.0	1.0, 65.0	1.0, 65.0	1.0, 65.0
0–4	28 (15.2%)	9 (11.5%)	–	–
5–11	77 (41.8%)	35 (44.9%)	49 (50.5%)	21 (52.5%)
12–18	36 (19.6%)	17 (21.8%)	20 (20.6%)	9 (22.5%)
Over 18	43 (23.4%)	17 (21.8%)	28 (28.9%)	10 (25.0%)
Standing height (cm)				
n	163	66	95	39
Mean (SD)	104.1 (16.82)	105.1 (15.96)	106.3 (14.16)	107.3 (12.60)
Median	99.5	101.0	101.9	102.0
Min, max	81.4, 171.5	82.0, 171.5	83.0, 150.5	90.0, 141.0
Weight (kg)				
n	184	78	97	40
Mean (SD)	24.5 (12.85)	25.9 (14.48)	26.1 (10.28)	26.8 (10.73)
Median	21.40	22.30	23.80	23.60
Min, max	10.2, 110.6	10.6, 110.6	12.2, 67.0	12.2, 67.0
6 MWT distance (m)				
n [b]	147	66	77	38
Mean (SD)	209.0 (132.59)	197.2 (131.36)	201.8 (83.73)	206.7 (81.32)
Median	220.5	209.5	206.9	218.3
Min, max	0.0, 531.0	0.0, 418.5	30.0, 320.0	60.0, 325.0
3 MSCT (steps/min)				
n [b]	134	55	72	33
Mean (SD)	30.3 (21.93)	27.0 (18.88)	30.7 (17.73)	28.7 (16.08)
Median	28.9	24.30	28.00	24.3
Min, max	0.0, 85.6	0.0, 73.5	0.0, 85.6	0.0, 60.4
FVC (L)				
n [b]	122	49	71	32
Mean (SD)	1.1 (0.76)	1.2 (0.78)	1.2 (0.70)	1.2 (0.60)
Median	0.90	1.0	0.9	1.0
Min, max	0.3, 4.7	0.2, 4.9	0.3, 4.7	0.2, 2.5
MVV (L/min)				
n [b]	106	44	63	29
Mean (SD)	32.2 (19.09)	34.7 (25.33)	32.9 (18.81)	31.5 (14.50)
Median	26.5	28.2	26.6	29.9
Min, max	7.0, 107.0	10.3, 160.0	7.0,103.0	10.3, 68.0
Urine KS (μg/mg) [c]				
n	180	78	97	40
Mean (SD)	37.57 (27.24)	36.46 (23.53)	33.48 (25.64)	31.21 (18.61)
Median	32.55	35.15	30.70	34.60
Min, max	0.94, 168.10	2.30, 102.70	2.30, 168.10	2.30, 68.40

Abbreviations: 6 MWT = 6 minute walk test; 3 MSCT = 3 minute stair climb test; FVC = forced vital capacity; MVV = maximum voluntary ventilation; KS = keratan sulfate.

[a] Phase 3-matched subjects are those subjects who met the inclusion/exclusion criteria of the Phase 3 clinical trial of elosulfase alfa, i. e. ≥5 years of age with baseline 6MWT distance ≥30 and ≤325 m.

[b] Only subjects with both baseline and follow-up data were included.

[c] Normalized urine KS values (calculated as urine KS divided by urine creatinine).

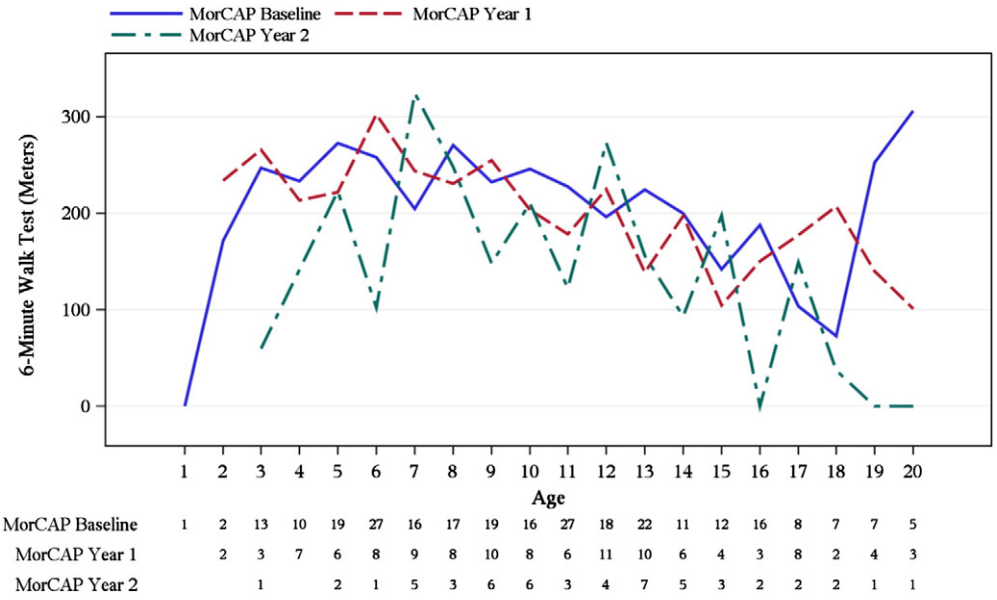

Fig. 1. Mean 6MWT distance versus age in MorCAP subjects aged ≤20 years.

3.2. 6MWT and 3MSCT

The majority of subjects within each group had an evaluable 6MWT at both baseline and at follow-up. Among these subjects, 30 were deemed physically unable to perform at least one 6MWT (scored as 0), the majority of whom were unable to perform the test both at baseline and all available follow-up; no reasons were given to explain the inability to perform a test. Twenty one subjects used a walking aid (cane, crutches, walking frame) during the test; changes in 6MWT were similar between those who used walk aids and those who did not. Several subjects were unable to complete a 6MWT due to pain (13 subjects), fatigue (7 subjects) and shortness of breath (4 subjects).

At each visit, mean 6MWT distances were found to generally decrease with increasing age (Fig. 1). Mean baseline 6MWT distances for the groups of subjects under evaluation ranged from 197.2 m to 209.0 m (Tables 1 and 2). The least-square mean changes in 6MWT distance from baseline are shown in Fig. 2 and are also summarized in Table 2. Declines from baseline 6MWT distances were observed at Year 1 and Year 2 and were more pronounced in the Phase 3-matched subjects. The annualized estimate of change (SE) in 6MWT from baseline across all subjects was −4.86 ± 3.25 m, while a greater decline of −6.84 ± 5.38 m was determined for the Phase-3 matched subjects (Table 2).

Most subjects within each group had an evaluable 3MSCT at both baseline and at follow-up. Of these subjects, 34 were considered physically unable to perform at least one 3MSCT (scored as 0); no reasons were given to explain an inability to perform the test. Some subjects were unable to complete a 3MSCT due to pain (4 subjects), fatigue (9 subjects) and shortness of breath (3 subjects).

Mean baseline 3MSCT for the groups ranged from 27.0 to 30.7 steps/min (Tables 1 and 2). The least-square mean changes in 3MSCT were small, ranging from −0.02 to −0.61 steps/min (Table 2). The annualized estimate of change (SE) in 3MSCT from baseline was −0.14 ± 0.60 steps/min across all subjects and −0.30 ± 0.99 steps/min for the Phase 3-matched subjects (Table 2).

3.3. FVC and MVV

Pulmonary function reference values are derived from individuals of normal stature, and therefore the utility of these values is unclear for individuals with severe short stature. Additionally, it is difficult to accurately assess height in these patients due to their severe skeletal dysplasia (severe genu valgum, scoliosis, etc.). For these reasons, FVC and MVV changes were analyzed in terms of percent change in absolute volumes rather than as percent predicted values. Mean percent changes from baseline FVC (1.1–1.2 L) and baseline MVV (31.5–34.7 L/min) are

Table 2
Summary of changes in 6MWT and 3MSCT.

	Mean (SD) baseline	Least square mean (SE) change from baseline	Annualized change (SE)
6MWT (m)			
All subjects			−4.86 (3.25)
With Year 1 follow-up (n = 147)	209.0 (132.59)	−3.92 (5.118)	
With Year 2 follow-up (n = 66)	197.2 (131.36)	−9.72 (6.499)	
Phase 3-matched subjects			−6.84 (5.38)
With Year 1 follow-up (n = 77)	201.8 (83.73)	−5.81 (7.868)	
With Year 2 follow-up (n = 38)	206.7 (81.32)	−13.67 (10.762)	
3MSCT (steps/min)			
All subjects			−0.14 (0.603)
With Year 1 follow-up (n = 134)	30.3 (21.93)	−0.02 (0.761)	
With Year 2 follow-up (n = 55)	27.0 (18.88)	−0.28 (1.206)	
Phase 3-matched subjects			−0.30 (0.987)
With Year 1 follow-up (n = 72)	30.7 (17.73)	−0.61 (1.222)	
With Year 2 follow-up (n = 33)	28.7 (16.08)	−0.60 (1.974)	

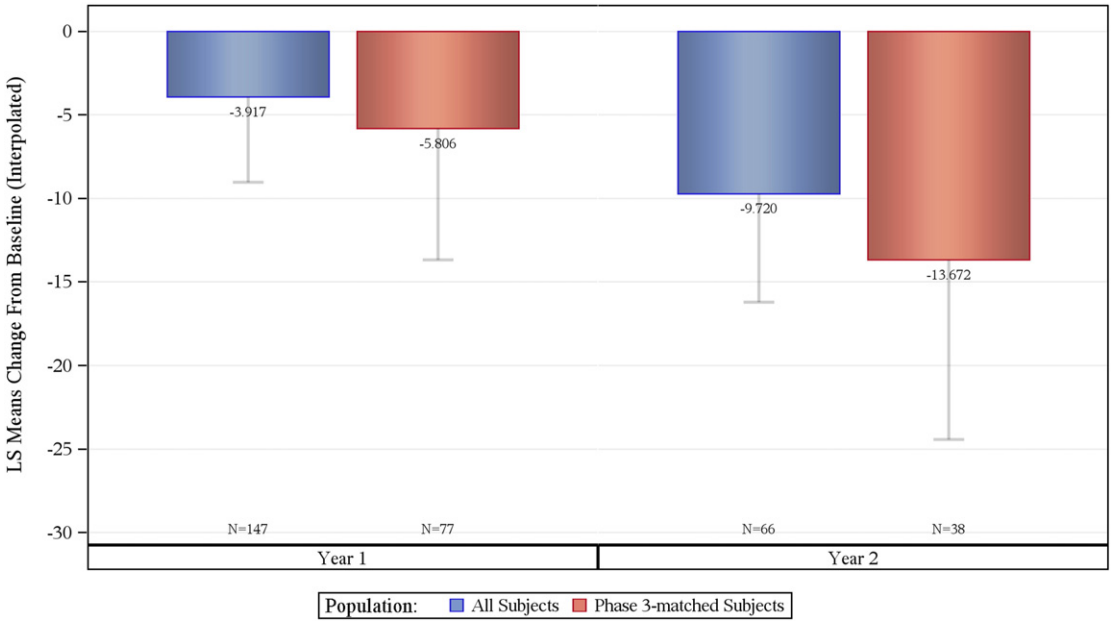

Fig. 2. Mean 6MWT changes from baseline for MorCAP subjects.

summarized in Table 3 and show trends towards an increase. The annualized estimates of change (SE) in FVC and MVV were 2.44 ± 0.68% and 1.01 ± 2.38%, respectively, across all subjects, and 2.39 ± 0.75% and 0.10 ± 2.69%, respectively, for the Phase 3-matched subjects (Table 3). Further analysis revealed that the longitudinal changes in these respiratory function parameters were age-dependent: FVC and MVV increased in subjects who were aged ≤14 years at baseline but decreased in older patients (Fig. 3). Changes in FVC or MVV did not correlate with changes in 6MWT (Fig. 4).

4. Discussion

Insight into the natural history of Morquio A syndrome is expected to guide clinical management strategies. Cross-sectional analysis of 325 MorCAP subjects at baseline demonstrated significant limitations in endurance and respiratory function and showed that impairments in 6MWT, 3MSCT, FVC and MVV were generally more severe in older patients [2]. Findings from this longitudinal analysis provide further evidence that untreated Morquio A syndrome is progressive and characterized by gradual decline in endurance and respiratory function parameters.

The 6MWT (or 12MWT as a variation) provides a simple and sensitive measure of the functional capacity of MPS patients and has been used as a primary outcome measure or component of a composite outcome measure in ERT clinical trials for MPS I, II, and VI, as well as Morquio A syndrome [16–20]. Mean baseline 6MWT distances for the subjects analyzed in this study were at least 2- to 3-fold below the lower limits of age-specific normal ranges reported for healthy children and adolescents [25–28] and for healthy adults [22,29]: one study reported a mean 6MWT distance of 470 ± 59 m for healthy boys and girls aged 4–11 years [26], while another reported a mean 6MWT distance of 618 ± 79 m for healthy children and adolescents aged 5–17 years [28]; for adults, mean 6MWT distances of 593 ± 57 m and 638 ± 44 m have been reported for healthy women and men, respectively [29]. The mean walk distances of MorCAP subjects were also considerably lower than those reported for populations of untreated patients with MPS I (319.1 ± 131.4 m to 366.7 ± 113.7 m), MPS II (392 ± 107 m to 401 ± 102 m), and MPS VI (273.1 ± 137.03 m) [16,17,30], and reflect the greater degree of musculoskeletal involvement in Morquio A patients. Moreover, mean 6MWT distance generally decreased with age, corroborating the findings from the cross-sectional analysis [2]; this trend is in sharp contrast to what is expected in unaffected populations of healthy children and adolescents [25,26,28]. A general decline in 6MWT distance from baseline was observed across all subjects over the course of this 2-year longitudinal study, indicating that Morquio A syndrome is characterized by progressive impairment in

Table 3
Summary of changes in FVC and MVV.

	Mean (SD) baseline	Least square mean % change (SE) from baseline	Annualized % change (SE)
FVC (L)			
All subjects			2.44 (0.678)
With Year 1 follow-up (n = 122)	1.1 (0.76)	2.05 (1.012)	
With Year 2 follow-up (n = 49)	1.2 (0.78)	4.88 (1.357)	
Phase 3-matched subjects			2.39 (0.747)
With Year 1 follow-up (n = 71)	1.2 (0.70)	2.10 (1.261)	
With Year 2 follow-up (n = 32)	1.2 (0.60)	4.78 (1.493)	
MVV (L/min)			
All subjects			1.01 (2.376)
With Year 1 follow-up (n = 106)	32.2 (19.09)	3.65 (4.506)	
With Year 2 follow-up (n = 44)	34.7 (25.33)	2.02 (4.752)	
Phase 3-matched subjects			0.10 (2.692)
With Year 1 follow-up (n = 63)	32.9 (18.81)	1.77 (4.114)	
With Year 2 follow-up (n = 29)	31.5 (14.50)	0.19 (5.384)	

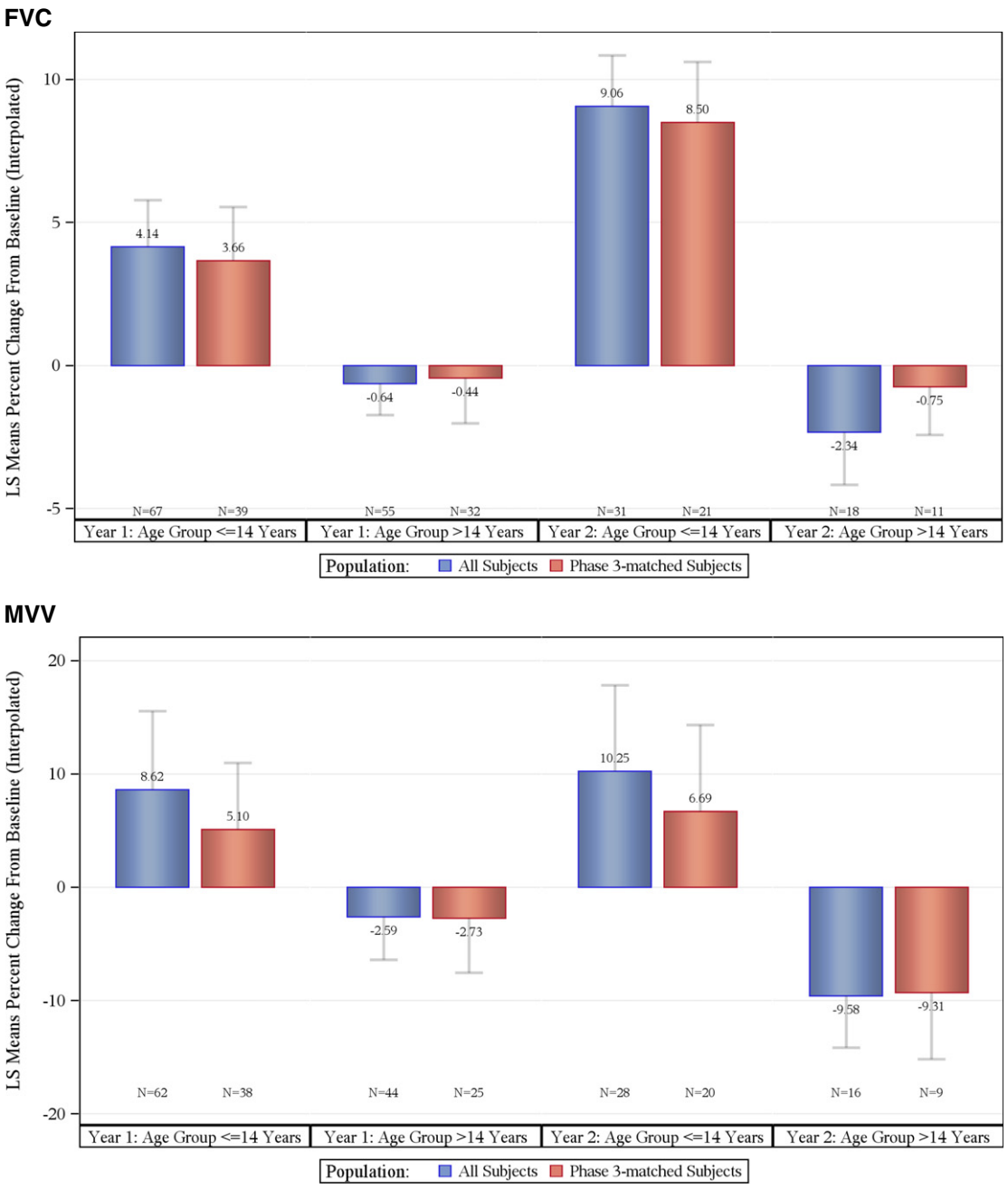

Fig. 3. FVC and MVV changes in MorCAP subjects stratified by baseline age ≤14 years and >14 years.

endurance and mobility. Patient quality of life is expected to worsen as mobility declines and wheelchair dependence increases [31]. While further study will be required to determine the exact mechanisms underlying the observed decline in walking ability, the results from this study demonstrate the utility of the 6MWT as a clinically meaningful measure of disease progression in ambulatory Morquio A patients.

It is unclear why a similar change in 3MSCT was not observed. It is possible that this test may not be suitable for Morquio A patients, who typically have severe skeletal dysplasia, short stature and joint involvement that considerably limit the ability to climb stairs. Difficulties with standardizing stair height and stairwell configuration may have also influenced the data.

Subjects showed significant impairment in respiratory function at baseline, with absolute FVC and MVV volumes comparable to those reported for other MPS disorders [17,30,32] and well below those reported for healthy subjects of normal stature [33–35]. The respiratory function compromise may be attributed to the combined effects of multiple abnormalities including short stature, altered chest wall shape and size, and airway obstruction [36]. While an overall upward trend was observed in respiratory function, the longitudinal changes in FVC and MVV were found to be dependent on age. Growth-related factors (height increase, thoracic enlargement) likely influence the observed patterns of change as FVC and MVV increased in patients with baseline age ≤14 years but decreased in older patients. In healthy children and adolescents, lung function measurements increase with height, with the greatest increase occurring during puberty [33]. It is likely, therefore, that overall declines in FVC and MVV will be observed in MorCAP subjects over a longer period of follow-up.

To better understand why the decline observed in 6MWT was not reflected in the respiratory function tests, an analysis of the correlation between these parameters was performed. No correlations between changes in 6MWT and respiratory function parameters were found in

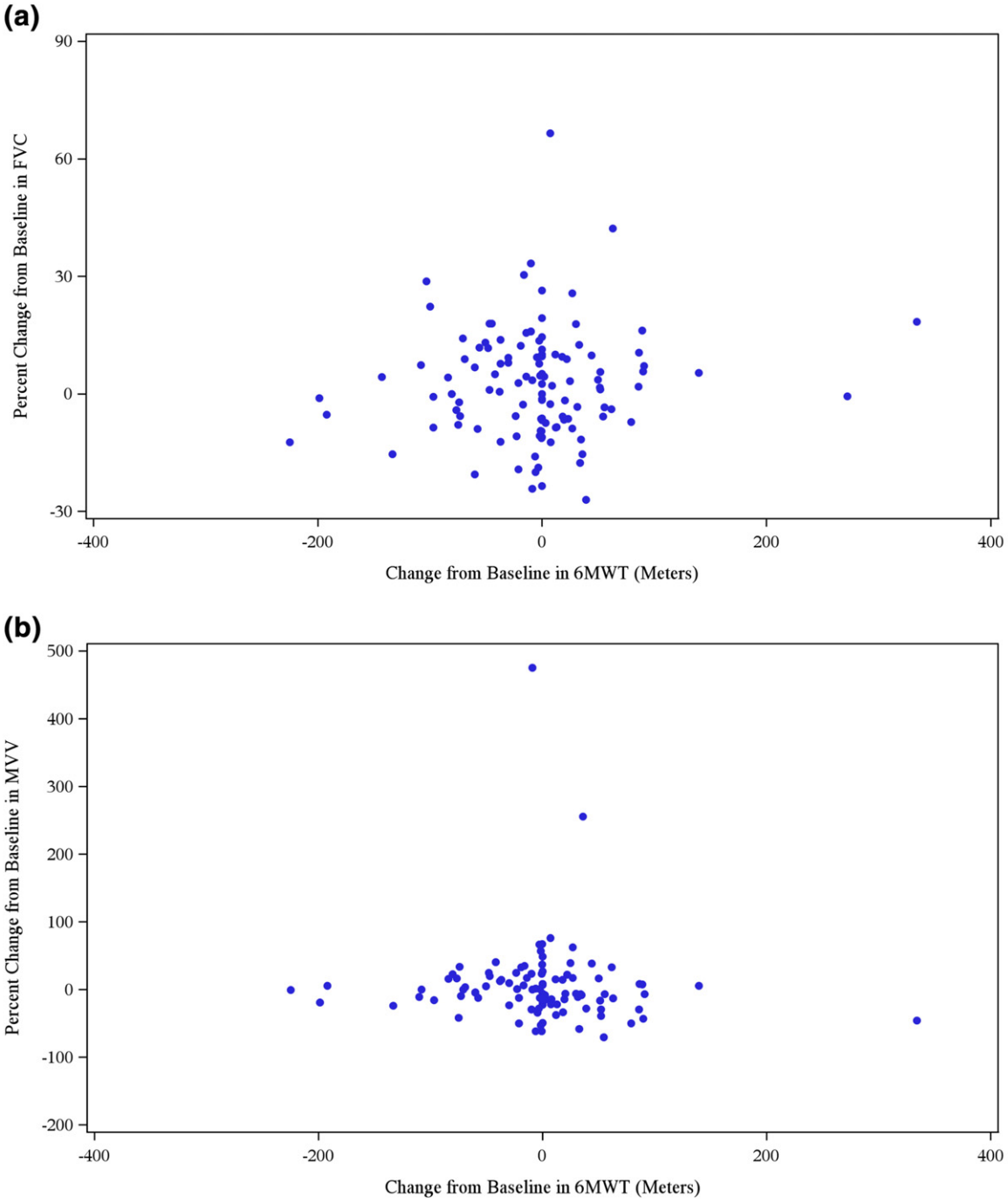

Fig. 4. Scatter plots of (a) percent change of FVC and change in 6MWT and (b) percent change of MVV and change in 6MWT. Data shown are for Year 1.

this study. This could be due to the fact that ventilatory demands are different in the 6MWT and respiratory function tests. The 6MWT is a submaximal exercise capacity test while FVC and MVV assessments require maximum effort. Alternatively, the 6MWT is multi-factorial and the observed decline may be predominantly driven by factors other than respiratory limitations. It is noteworthy that several (13) subjects could not complete the 6MWT due to pain, suggesting that the influence of musculoskeletal impairment is significant. Other reasons cited for incompletion of a 6MWT were fatigue and shortness of breath. Longer duration of follow-up as well as inclusion of assessments of pain, fatigue, shortness of breath and other relevant physical factors before and after testing are likely to yield more insight into the determinants of the observed decline in 6MWT distance.

There were several limitations associated with this study. Many subjects left the MorCAP study to enroll in ERT clinical trials, resulting in a smaller study population and less precise estimates of endurance and respiratory changes. Limited assessments were conducted before and after the 6MWT; formal evaluations of pain or fatigue, for example, could have been helpful in elucidating the mechanisms for the observed decline. Due to the degree of respiratory compromise in this population, some recorded values may have been a result of unsatisfactory effort. While the scope of this study was limited to focus on key clinical endpoints relevant to the ERT trials, future analyses are planned to analyze other parameters collected in MorCAP as well as to define possible associations between urinary keratan sulfate levels and changes in clinical parameters. Longer follow-up and further analyses will be needed to

identify the factors that influence longitudinal trends in endurance and respiratory function parameters.

5. Conclusions

Untreated Morquio A syndrome is characterized by progressive decline in endurance as measured by the 6MWT. Changes in 6MWT may represent a sensitive measure of disease progression in ambulatory Morquio A patients. Growth likely influences the longitudinal patterns of change in respiratory function, as FVC and MVV parameters increased in younger patients but decreased in older patients. Longer duration of follow-up will be required to elucidate the natural history of Morquio A syndrome.

Conflicts of interest

P. R. Harmatz has provided consulting services, received research grants, participated in advisory board meetings and received speaker honoraria and travel support from BioMarin Pharmaceutical Inc. (BioMarin). K. Yang, P. Slasor and C. Decker are employees and stockholders of BioMarin. All other authors are investigators and/or consultants of BioMarin, have received research grants from BioMarin, and have received travel support from BioMarin.

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