Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human *N*-acetylgalactosamine 4-sulfatase

Paul Harmatz · Zi-Fan Yu · Roberto Giugliani · Ida Vanessa D. Schwartz ·
Nathalie Guffon · Elisa Leão Teles · M. Clara Sá Miranda · J. Edmond Wraith ·
Michael Beck · Laila Arash · Maurizio Scarpa · David Ketteridge · John J. Hopwood ·
Barbara Plecko · Robert Steiner · Chester B Whitley · Paige Kaplan ·
Stuart J. Swiedler · Karen Hardy · Kenneth I. Berger · Celeste Decker

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Abstract Pulmonary function is impaired in untreated mucopolysaccharidosis type VI (MPS VI). Pulmonary function was studied in patients during long-term enzyme replacement therapy (ERT) with recombinant human arylsulfatase B (rhASB; rh*N*-acetylgalactosamine 4-sulfatase). Pulmonary function tests prior to and for up

to 240 weeks of weekly infusions of rhASB at 1 mg/kg were completed in 56 patients during Phase 1/2, Phase 2, Phase 3 and Phase 3 Extension trials of rhASB and the Survey Study. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and, in a subset of patients, maximum voluntary ventilation (MVV), were

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The authors are reporting for the MPS VI Study Group; see Acknowledgments for list of co-investigators.

P. Harmatz (✉) · K. Hardy
Children's Hospital & Research Center Oakland,
747 52nd Street,
Oakland, CA 94609, USA
e-mail: Pharmatz@mail.cho.org

Z.-F. Yu
Statistics Collaborative, Inc,
Washington, DC, USA

R. Giugliani · I. V. D. Schwartz
Medical Genetics Service/ HCPA and Department of Genetics/
UFRGS,
Porto Alegre, Brazil

N. Guffon
Hôpital Femme Mère Enfant, Service Maladies Métaboliques,
Bron, France

E. L. Teles
Departamento Pediatria, Hospital de Sao João,
Unidade de Doenças Metabólicas,
Porto, Portugal

M. C. S. Miranda
Instituto de Biologia Molecular e Celular,
Unidade de Biologia do Lisossoma e Peroxisoma,
Porto, Portugal

J. E. Wraith
Royal Manchester Children's Hosp,
Manchester, UK

M. Beck · L. Arash
Children's Hosp, University of Mainz,
Mainz, Germany

M. Scarpa
Department of Pediatrics,
University of Padova,
Padova, Italy

D. Ketteridge
SA Pathology at Women's and Children's Hospital,
North Adelaide, SA, Australia

analyzed as absolute volume in liters. FEV1 and FVC showed little change from baseline during the first 24 weeks of ERT, but after 96 weeks, these parameters increased over baseline by 11% and 17%, respectively. This positive trend compared with baseline continued beyond 96 weeks of treatment. Improvements from baseline in pulmonary function occurred along with gains in height in the younger group (5.5% change) and in the older patient group (2.4% change) at 96 weeks. Changes in MVV occurred earlier within 24 weeks of treatment to approximately 15% over baseline. Model results based on data from all trials showed significant improvements in the rate of change in pulmonary function during 96 weeks on ERT, whereas little or no improvement was observed for the same time period prior to ERT. Thus, analysis of mean percent change data and longitudinal modeling both indicate that long-term ERT resulted in improvement in pulmonary function in MPS VI patients.

Abbreviations

MPS VI	Mucopolysaccharidosis VI
rhASB	Recombinant human arylsulfatase B
ERT	Enzyme replacement therapy
GAG	Glycosaminoglycans
FVC	Forced vital capacity
FEV1	Forced expiratory volume in 1 s
MVV	Maximum voluntary ventilation
LME	Longitudinal linear mixed-effects model

J. J. Hopwood
Department of Genetic Medicine,
Women's and Children's Hospital Adelaide,
North Adelaide, SA, Australia

B. Plecko
Univ. Klinik für Kinder und Jugendheilkunde,
Graz, Austria

R. Steiner
Departments of Pediatrics and Molecular and Medical Genetics,
Oregon Health & Science University,
Portland, OR, USA

C. B. Whitley
University of Minnesota Medical School,
Minneapolis, MN, USA

P. Kaplan
Children's Hospital of Philadelphia,
Philadelphia, PA, USA

S. J. Swiedler · C. Decker
BioMarin Pharmaceutical Inc,
Novato, CA, USA

K. I. Berger
Departments of Medicine, Physiology and Neuroscience,
New York University School of Medicine,
New York, NY, USA

Introduction

Mucopolysaccharidosis type VI (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disease in which deficient activity of the enzyme *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B, or ASB; E.C # 3.1.6.12) impairs the stepwise degradation of the glycosaminoglycan (GAG) dermatan sulfate (DS) (Giugliani et al. 2007). Partially degraded GAG accumulates in lysosomes and in a wide range of tissues, causing a chronic progressive disorder characterized by significant functional impairment and a shortened lifespan.

A survey of 121 MPS VI affected individuals found that high urinary GAG values (>200 µg/mg creatinine) were associated with an accelerated clinical course including reduced endurance, greater pulmonary function impairment, and lower height values for age (Swiedler et al. 2005). Impairment in endurance based on a 6-min walk test was observed across all age groups and levels of GAG accumulation.

Three enzyme replacement therapy (ERT) studies using recombinant human ASB (known as rhASB ; recombinant human *N*-acetylgalactosamine 4-sulfatase; galsulfase; Naglazyme®) to treat patients with MPS VI have been reported. A Phase 1/2 study and a Phase 2 study both demonstrated that weekly infusions of 1 mg/kg rhASB were well tolerated, produced a rapid reduction in urinary GAG levels, and improved endurance in patients with rapidly advancing disease (Harmatz et al. 2004; Harmatz et al. 2005). A Phase 3 double-blind, placebo-controlled study demonstrated greater improvement in endurance on the 12-min walk test (12MWT) in patients treated with rhASB for 24 weeks compared with patients receiving placebo (Harmatz et al. 2006). In all studies, improvement in endurance was maintained during the open-label extension phase for up to 240 weeks, with an acceptable safety profile (Harmatz et al. 2008). In addition to endurance measures, all three studies included pulmonary function assessments. The mechanism for this improved endurance is unknown but may relate to an impact of ERT on pulmonary function.

The purpose of this paper is to evaluate pooled long-term data from the clinical ERT trials and the Survey Study to determine the impact of ERT on pulmonary function in patients with MPS VI.

Methods

Study design

Detailed study design and evaluation criteria have been reported in previous publications of the MPS VI Survey

Study and the Phase 1/2, Phase 2, and Phase 3 clinical studies of rhASB (galsulfase, Naglazyme) treatment in MPS VI, which reported results of 48 weeks of treatment (Harmatz et al. 2004; Harmatz et al. 2005; Harmatz et al. 2006). Collection of efficacy data continued for up to 240 weeks during the extension phase of these studies. Pretreatment data were specifically collected from patients in the Survey Study and placebo-treated patients in the first 24 weeks of the Phase 3 clinical trial. These studies are summarized in Table 1. An Institutional Review Board (IRB) or Ethics Committee (EC) at each participating clinical site approved each study. All adult patients and parent/guardians gave written consent; patients younger than 18 years old gave written assent according to local IRB regulations.

All patients received rhASB at 1 mg/kg/week infused over a 4-h period, except three patients in the Phase 1/2 study who received 0.2 mg/kg per week for the initial part of that study and 19 patients who completed the Phase 3 study. These 19 patients received placebo during the blinded portion of the Phase 3 study and received rhASB for the open-label remainder of the study (weeks 24–96). These patients underwent evaluations following 24 and 72 weeks of active therapy, i.e., at weeks 48 and 96 of the study. Assessments were completed for each study group as shown in Table 2.

Pulmonary function parameters examined during all studies included forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). Data were obtained in accord with the American Thoracic Society guidelines (1995). The Phase 3 study also measured the maximum voluntary ventilation (MVV), which was defined as the maximum volume of air that can be breathed in 1 min. Data were collected while the patients breathed as deeply and quickly as possible for 15 s and then were extrapolated to 1 min (American Thoracic Society guidelines 1991).

Analysis methods

This analysis focused on long-term pulmonary function outcomes in patients receiving ERT over an extended period. In addition, the pooled data were analyzed to determine: (1) the importance of height change on the mean improvement in pulmonary function during ERT, and (2) the mean rate of increase in pulmonary function parameters prior to and following ERT initiation. To evaluate the improvement in pulmonary function relative to growth, pooled data were stratified into two groups: patients <12 years versus patients ≥12 years at treatment initiation. The age of 12 years was chosen to approximate the midpoint of normal pubertal development, and it is assumed that patients who started ERT after this age are less likely to experience significant growth. In each age group, mean percent change in FVC, FEV1, and height were analyzed.

Table 1 Summary of study populations

Study	Study design	Study time period (years)	Duration of efficacy evaluations (weeks)	Number of patients enrolled/completed	Dose of rhASB mg/kg	Age (years) mean±SD (range years)	Sex (M/F)	Height (cm) mean±SD	Number of patients withdrawn: time of withdrawal	Baseline urinary GAG (μg/mg creatinine) mean±SD
Phase 1/2	Double-blind, randomized, dose comparison/open-label extension	2001–2005	240	7/5	0.2 1.0	12.0±3.8 (7–16)	4/3	107.5±21.5	1 (0.2 mg/kg) after week 3; 1 (0.2 mg/kg) after week 32	365±148
Survey study (patients not on ERT)	Cross-sectional study of patients not on ERT	2002–2003		123/121	None	13.9±10 (4–56)	58/63	115±26		321±200
Phase 2	Open-label, nonrandomized	2002–2006	144	10/10	1.0	12.1±5.3 (6–21)	7/3	103.7±14.4	0	336±116
Phase 3	Double-blind, placebo-controlled, randomized/open-label extension	2003–2006	96	39/38	1.0	13.7±6.5 (rhASB) 10.7±4.4 (placebo) (5–29)	13/26	104.4±2.9 (rhASB) 100.3±13.5 (placebo)	1 (placebo group) after week 5	346±128 (rhASB) 330±114 (placebo)

Table 2 Schedule of assessments

Study	Evaluation	Treatment week							
		0	24	48	72	96	144	192	240
Phase 1/2	FVC	X	X	X		X	X	X	X
	FEV1	X	X	X		X	X	X	X
	Height	X	X	X		X	X	X	X
Phase 2	FVC	X	X	X	X	X	X	PSC	PSC
	FEV1	X	X	X	X	X	X	PSC	PSC
	Height	X	X	X	X	X	X	PSC	PSC
Phase 3 rhASB/rhASB	FVC	X	X	X		X	PSC	PSC	PSC
	FEV1	X	X	X		X	PSC	PSC	PSC
	MVV	X	X	X		X	PSC	PSC	PSC
	Height	X	X	X	X	X	PSC	PSC	PSC
Phase 3 placebo/rhASB	FVC	X	X		X	PSC	PSC	PSC	PSC
	FEV1	X	X		X	PSC	PSC	PSC	PSC
	MVV	X	X		X	PSC	PSC	PSC	PSC
	Height	X	X	X	X	PSC	PSC	PSC	PSC

Phase 1/2 had no week 72 but had week 84 PFT height assessments. PSC, post-study completion

To determine the mean rate of increase in pulmonary function parameters prior to and following initiation of ERT, a longitudinal linear mixed-effects model (LME) was constructed using pooled data. The model incorporated both pre-ERT and post-ERT data by including a linear spline for time with a knot at treatment week 0. This formulation allows different slopes of the mean trend before and after ERT initiation. A random intercept gives all individuals their own regression lines with separate intercepts that deviate from the population line. The longitudinal model includes repeated measures over time and allows observations within a patient to be correlated. The model uses empirical estimates for the standard error, which in large samples “corrects” for misspecifying the correlation structure. The model also includes baseline height as a covariate.

“Time” refers to time from ERT initiation. Because data were also obtained before the start of treatment, time includes negative values. The length of follow-up for each trial phase differs; most patients have at least 72–96 weeks of follow-up after ERT initiation, and the LME method is flexible in that patients do not have to have all measurements at all time points. The availability of pretreatment data is also limited; analysis therefore restricts the length of time to approximately a 2-year window on either side of ERT initiation.

Results

Baseline data

The age of patients at time of enrollment in a clinical therapy trial ranged from 5 to 29 years; the mean age was approximately 12 years. An overview of baseline height and pulmonary function data is presented in Table 3. As expected, patients <12 years were shorter on average than patients in the older age group, with a mean height of 99.4 cm versus 105.4 cm, respectively. Pulmonary function parameters were significantly impaired for age in comparison with a healthy population (Rosenthal et al. 1993). The younger group showed mean values for FVC and FEV1 of 0.56 L and 0.52 L, respectively, whereas the older group showed similar mean values of 0.55 L and 0.48 L, respectively, for the same measures.

Mean observed improvement in pulmonary function (FEV1, FVC, and MVV) during ERT

Data showing mean percent change in FEV1, FVC, and MVV during ERT are presented in Fig. 1. Changes from baseline in FEV1 and FVC were minimal up to 24 weeks of

Table 3 Combined Phase 1, Phase 2, and Phase 3 data: baseline height and pulmonary function

	All patients; mean (range)	Number	Age <12years; mean (range)	Number	Age ≥12years; mean (range)	Number
Height (cm)	101.9 (81.5, 136)	54	99.4 (81.5, 133)	32	105.4 (86, 136)	22
FVC (L)	0.56 (0.16, 1.74)	53	0.56 (0.16, 1.64)	32	0.55 (0.28, 1.74)	21
FEV1 (L)	0.50 (0.16, 1.67)	53	0.52 (0.16, 1.42)	32	0.48 (0.25, 1.67)	21

Fig. 1 Mean percent change in FVC, FEV1, and MVV by treatment week over all available patient data

treatment with rhASB but increased thereafter through 96 weeks of treatment. For FVC and FEV1, those on treatment for 72 weeks improved 14% from baseline on average ($p < 0.001$) for both outcomes. Those on treatment for 96 weeks improved approximately 17% ($p = 0.009$) and 11% ($p = 0.014$), respectively, relative to baseline. Changes in MVV occurred earlier. At 24 weeks of treatment, MVV increased approximately 15% over baseline ($p = 0.021$). Although sample sizes beyond 144 weeks of treatment were too small to make valid inferences, this trend of pulmonary function improvement compared with baseline appears to continue through 240 weeks of treatment.

Pulmonary function improvement from baseline relative to growth

In order to examine whether the observed change in pulmonary function could be attributed to growth, we examined pulmonary function after dividing the population into two groups based on age at time of treatment initiation: older or younger than 12 years (Table 4; Fig. 2). The left panel of Fig. 2 graphs data obtained in patients < 12 years. Both FEV1 and FVC showed little change from baseline during the first 24 weeks of ERT. By 96 weeks of treatment, these parameters showed meaningful improvement, with increases in FEV1 and FVC averaging approximately 10% and 13%, respectively, with respect to baseline. Height increased concomitantly with increases in FEV1 and FVC in the younger age group.

The right panel of Fig. 2 graphs similar data in older patients (age ≥ 12 years). As with the younger patients,

FEV1 and FVC did not improve relative to baseline in the first 24 weeks but showed meaningful improvement in subsequent weeks. For those on 96 weeks of treatment, FEV1 and FVC improved from baseline by approximately 13% and 23%, respectively. However, in contrast to the younger patient group, improvements in FEV1 and FVC seen in older patients occurred despite a smaller percent increase in height.

Mean rate of increase in pulmonary function parameters (FVC, FEV1) prior to and following ERT initiation

The observed increases over time during ERT are described using longitudinal modeling of the absolute changes in lung function relative to baseline, defined as the week prior to ERT initiation. The longitudinal models used all available pre-ERT and post-ERT data.

Regression analyses

Model results showed improvements for all patients on ERT compared with before ERT (Table 5; Fig. 3). For FEV1, the estimated mean value for all patients at baseline was 0.49 L. For approximately 2 years prior to ERT, mean FEV1 increased only 0.01 L on average. In contrast, over 2 years on ERT, mean FEV1 increased 0.06 L on average ($p < 0.001$) (Table 5). This improvement in FEV1 corresponds to an increase of approximately 12% relative to baseline value. When patients were subdivided into those < 12 years versus ≥ 12 years, the change in FEV1 post-ERT still remained, corresponding to approximately

Table 4 Combined Phase 1, Phase 2, and Phase 3 data: percent change height and pulmonary function from start of ERT by age group

Treatment week	Number ^a	FEV1 (L)		FVC (L)		Height (cm)		
		Observed mean (SD)	% Change mean (SD)	Observed mean (SD)	% Change mean (SD)	n	Observed mean (SD)	% Change mean (SD)
Age <12 years								
0	32	0.52 (0.26)	–	0.56 (0.31)	–	32	99.4 (11.1)	–
24	32	0.52 (0.31)	0.96 (21.0)	0.57 (0.37)	1.5 (21.7)	32	101.0 (11.2)	1.6 (1.1)
48	17	0.62 (0.41)	7.1 (32.5)	0.69 (0.48)	6.8 (32.0)	30	102.9 (11.4)	3.6 (1.6)
72	20	0.55 (0.30)	15.3 (18.1)	0.57 (0.21)	17.5 (20.0)	29	103.4 (11.2)	4.9 (1.7)
96	17	0.64 (0.44)	9.6 (28.8)	0.73 (0.51)	12.5 (32.9)	27	105.7 (11.8)	5.5(2.1)
144	7	0.75 (0.41)	11.1 (15.4)	0.91 (0.48)	17.6 (11.6)	9	110.6 (13.6)	8.6 (2.4)
192	3	0.73 (0.35)	16.4 (21.6)	0.99 (0.49)	39.6 (14.7)	3	116.2 (16.0)	8.6 (3.9)
240	3	0.70 (0.30)	13.6 (12.1)	0.98 (0.48)	39.8 (12.0)	3	120.2 (17.0)	12.2 (3.1)
Age ≥12 years								
0	21	0.48 (0.30)	–	0.55 (0.32)	–	22	105.4 (12.8)	–
24	21	0.49 (0.29)	2.6 (14.6)	0.54 (0.32)	–2.0 (9.6)	22	106.3 (12.5)	0.9 (1.4)
48	17	0.54 (0.32)	8.2 (16.0)	0.60 (0.22)	5.2 (17.6)	20	109.1 (11.8)	1.8 (1.7)
72	8	0.47 (0.19)	9.7 (9.6)	0.52 (0.22)	6.5 (7.3)	17	109.9 (12.6)	2.7 (2.1)
96	16	0.57 (0.32)	12.9 (20.4)	0.74 (0.49)	22.6 (39.0)	19	110.2 (12.4)	2.4 (2.9)
144	7	0.49 (0.22)	17.0 (27.4)	0.57 (0.21)	20.2 (20.9)	10	107.9 (10.3)	1.2 (2.1)
192	2	0.47 (0.02)	35.9 (3.6)	0.52 (0.06)	49.0 (22.2)	2	96.5 (3.5)	-1.5 (1.5)
240	2	0.39 (0.03)	14.5 (16.5)	0.46 (0.08)	30.6 (27.5)	2	100.1 (6.3)	2.0 (2.4)

Patient population will not necessarily include exactly the same patients at each timepoint.

^a Percent change FEV1 and FVC have same n

14% in the younger group and 11% in the older group (refer to Table 5; small differences in percentages between text and Table 5 are related to actual data versus modeled data).

For FVC, the estimated mean for all patients at baseline was 0.54 L. In the 2 years prior to ERT, mean FVC increased approximately 0.01 L on average. In contrast, over 2 years on ERT, mean FVC increased 0.10 L on average ($p < 0.001$) (Table 5). This improvement in FVC corresponds to an increase of approximately 19% relative to baseline value. Both younger and older groups demonstrated improvement in FVC after treatment (approximately 14% and 25%, respectively) compared with lesser improvements before treatment (refer to Table 5). For all parameters, the younger group showed minimal or no improvement prior to treatment, with significant improvement after ERT initiation. Older patients demonstrated minor improvement in lung function pre-ERT, with significant improvement after ERT (Table 5).

Discussion

Studies have demonstrated that ERT with rhASB leads to a sustained improvement in endurance in the MPS VI patient population (Harmatz et al. 2008). An important factor

contributing to improved endurance is likely to be pulmonary function. In this study, analysis of pooled pulmonary function data from rhASB clinical studies shows that MPS VI patients on ERT demonstrated improvement from baseline in pulmonary function that was sustained over long-term treatment and occurred independent of age. Whereas the improvement in pulmonary function may be in part related to growth in the younger patients, the pulmonary function improvement seen in older patients occurred with smaller change in height and may be attributed to other mechanical, anatomical, or physiological factors influencing lung function.

Consistent with previously reported findings in individual MPS VI clinical trials, analysis of combined data did not show mean percent improvement in FVC and FEV1 over the short term (24 weeks). However, by 72 or 96 weeks of treatment, both FVC and FEV1 showed improvement from baseline of at least 11%. For individuals with normal lung function, a 15% relative increase in FEV1 year to year is considered a clinically meaningful change according to the American Thoracic Society guidelines (1991) (Pellegrino et al. 2005). It is important to note that we examined improvement in pulmonary function in terms of absolute volume, not percent predicted. These gains could not be expressed in terms of percent predicted ($[\text{actual result}/\text{predicted result}] \times 100\%$), as a standard curve does not exist for this population, which

Fig. 2 Mean percent change in height and pulmonary function by treatment week and age group over all available patient data

is similar to the achondroplasia patient population in which small stature and dysplastic bone changes confound calculation of these percentages (Stokes et al. 1988; 1990).

In contrast to the delayed improvement in traditional pulmonary function measures of FVC and FEV1, the MVV showed rapid improvement relative to baseline over 24 weeks. The MVV maneuver of rapid respiration is

thought to replicate maximal ventilation during exercise (Stein et al. 2003). Although MVV is generally well correlated with FEV1 (Fulton et al. 1995; Stein et al. 2003), a disproportionate decrease in MVV relative to FEV1 has been reported in neuromuscular disorders (Serisier et al. 1982; Braun et al. 1983) and upper airway obstruction (Engstroem et al. 1964), and therefore, im-

Table 5 Predicted changes over 2 years based on longitudinal model results

	Model	Predicted mean at baseline	Time period	N	Predicted change over 2 years (SE)	P value
FEV1 (L)	All patients	0.49	Pre-ERT	35	0.01±0.03	0.84
			Post-ERT	53	0.06±0.02	<0.001
	Age <12 years	0.51	Pre-ERT	22	0.00±0.02	0.93
			Post-ERT	32	0.07±0.02	0.005
	Age ≥12 years	0.46	Pre-ERT	13	0.02 ±0.07	0.81
			Post-ERT	21	0.05±0.02	0.027
FVC (L)	All patients	0.54	Pre-ERT	35	0.01±0.03	0.71
			Post-ERT	53	0.10±0.03	<0.001
	Age <12 years	0.56	Pre-ERT	22	-0.02±0.02	0.47
			Post-ERT	32	0.08±0.02	0.001
	Age ≥12 years	0.51	Pre-ERT	13	0.07±0.09	0.41
			Post-ERT	21	0.13±0.06	0.036

Fig. 3 Observed FVC (L) and modeled regression line. Dots show the scatter of all patients' FVC measurements over time

provement in these areas with ERT may contribute to the earlier response on the MVV assessment.

The mechanism for the observed improvement in lung function during ERT and its relationship to growth is of interest. In this study, lung function improved relative to baseline to a similar extent in younger and older age groups, suggesting height did not determine this improvement. Observations in other MPS disorders during ERT suggest that the improvement in lung function in older patients may be due to multiple mechanisms, including decreased upper airway obstruction as evidenced by improvement in sleep apnea severity, increased chest wall compliance as evidenced by improved joint mobility, and improved respiratory muscle strength and endurance as well as improved diaphragmatic excursion as evidenced by reduction in liver size (Wraith et al. 2004; Clarke et al. 2009). In younger patients, all of these mechanisms may apply, and height/thoracic enlargement may have an additive effect on FVC and FEV1.

A limitation of examining mean percent change data by treatment week is that the number of patients does not

remain consistent across all data points due to variations in design and length of the three clinical trials, potentially distorting the magnitude of changes over time. To minimize this effect, longitudinal modeling was chosen to estimate improvement trends at 96 weeks pre-ERT and post-ERT initiation. Modeled results in Table 5 do not reflect significant improvement pre-ERT but do show significant improvement post-ERT. In general, the magnitude of the changes did not differ greatly in the younger and older age groups, demonstrating that pulmonary function improvement occurs in ERT-treated patients regardless of age at treatment initiation.

There are several factors that may have influenced the results of the longitudinal modeling. In the pre-ERT data, comprising data that were collected in the Survey Study and from placebo patients in the Phase 3 study, some individuals had only one or two observations within the 2-year period prior to ERT initiation. Because these data tend to be variable, additional observations over time may have given a more accurate estimate of lung function during this time period. It is reassuring, then, that these data were collected in a controlled clinical setting and that the standard errors for pre-ERT versus post-ERT estimates of lung function are similar in both time periods. In addition, the number of patients with data beyond 96 weeks was limited, and thus, the observed trends should not be extrapolated beyond the range of data presented. Because the observed data showed a gradual improvement over time, a linear trend for modeling was chosen as a simple way to see whether the rate of improvement differed during the 2 years pre-ERT and post-ERT initiation. Individual patients may deviate from this trend, especially if growth and/or puberty occurred during treatment. In addition, longer-term follow-up (>2 years) may suggest more distinct nonlinear trends, but in this study, these would be difficult to detect or differentiate from random variation.

In this study, we cannot rule out the effect of growth on FVC. Whereas we considered including growth—i.e., time-varying height—in our model, several issues limited this possibility. Treatment with ERT may affect lung function through several causal pathways: it may have a direct and independent effect on lung function, or increase height, which in turn changes lung function. In the second scenario, height may be an intermediate variable in the causal pathway for lung function, particularly for FVC. As a result, a statistical model that controls for time-varying height may be inappropriate; it would likely obscure any effect of treatment that was mediated by height. Accordingly, we considered only baseline height in our model rather than height over time (i.e., growth).

In conclusion, progressive impairment in pulmonary function is characteristic of MPS VI disease, and a

significant amount of morbidity and mortality is attributable to respiratory complications (Simmons et al. 2005). The study presented here suggests by multiple statistical techniques that this trend toward decline in pulmonary function can be halted and partially reversed during ERT with *N*-acetylgalactosamine 4-sulfatase (rhASB, galsulfase, Naglazyme) over a period of 96 weeks of therapy. It is likely that this improvement is one factor underlying the increase in endurance documented in the 6-min and 12-min walk tests, although changes in pulmonary function appear to be delayed relative to improvement in endurance that is evident by 24 weeks of ERT (Harmatz et al. 2008). This improvement in respiratory function relative to baseline may lead to a decrease in the severity of respiratory illnesses and number of hospitalizations, and an overall improvement in the quality of life of MPS VI patients.

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The MPS VI Study Group co-investigators are: **John Waterson**, MD, PhD and **Elio Gizzi**, MD, Children's Hospital & Research Center Oakland, Oakland, California; **Yasmina Amraoui**, MD, Children's Hosp, University of Mainz, Germany; **Bonito Victor**, MD, Unidade de Doenças Metabólicas, Departamento Pediatria, Hospital de Sao João, Porto, Portugal; **Javier Arroyo**, MD, Hospital San Pedro de Alcantara, Hospital de día de Pediatria, Cáceres, Spain; **D.N. Bennett-Jones**, MD, Consultant General & Renal Physician, Whitehaven, UK; **Philippe Bernard**, MD, Centre Hospitalier d'Arras, Arras, France; Prof. **Billette de Villemeur**, Hôpital Trousseau, Paris, France; **Raquel Boy**, MD, Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil; **Eduardo Coopman**, MD, Hospital del Cobre De. Salvador, Calama, Chile; Prof. **Rudolf Korinthenberg**, Universitätsklinikum Freiburg, Zentrum für Kinderheilkunde und Jugendmedizin, Klinik II Neuropädiatrie und Muskelerkrankungen, Freiburg, Germany; **Michel Kretz**, MD, Hôpital Civil de Colmar, Le Parc Centre de la Mère et de l'Enfant, Colmar, France; **Shuan-Pei Lin**, MD, MacKay Memorial Hospital, Department of Genetics, Taipei, Taiwan; **Ana Maria Martins**, MD, UNIFESP, Instituto de Oncologia Pediátrica, GRAACC/UNIFESP, Departamento de Pediatria, São Paulo, Brazil; **Anne O'Meara**, MD, Our Lady's Hospital for Sick Children, Dublin, Ireland; **Gregory Pastores**, MD, PhD, NYU Medical Center, Rusk Institute, New York, New York; **Lorenzo Pavone**, MD, **Rita Barone**, MD, **Agata Fiumara**, MD, and Prof. **Giovanni Sorge**, Department of Pediatrics, University of Catania, Catania, Italy; **Silvio Pozzi**, MD, Ospedale Vito Fazzi, UO Pediatria, Lecce, Italy; **Uwe Preiss**, MD, Universitätsklinik und Poliklinik für Kinder, Halle, Germany; **Emerson Santana Santos**, MD, Fundação Universidade de Ciências da Saúde de Alagoas Governador, Departamento de Pediatria, Maceió, Brazil; **Isabel Cristina Neves de Souza**, MD and **Luiz Carlos Santana da Silva**, PhD, Universidade Federal do

Pará, Centro de Ciências Biológicas, Hospital Universitário João de Barros Barreto, Belém, Brazil; **Eugênia Ribeiro Valadares**, MD, PhD, Hospital das Clínicas, Faculdade de Medicina da Universidade Federal de Minas Gerais-UFMG, Avenida Professor Alfredo Balena, Belo Horizonte-Minas Gerais, Brazil; **Laura Keppen**, MD, Department of Pediatrics, University of South Dakota School of Medicine, Sioux Falls, SD; **David Silience**, MD, Children's Hospital, Westmead, Australia; **Lionel Lubitz**, MD, Royal Children's Hospital, Melbourne, Australia; **William Frischman**, MD, The Townsville Hospital, Townsville, Australia; **Julie Simon**, RN, Children's Hospital & Research Center Oakland, Oakland, California; **Claudia Lee**, MPH, Children's Hospital & Research Center Oakland, Oakland, California; **Stephanie Oates**, RN Department of Genetic Medicine, Women's and Children's Hospital Adelaide, North Adelaide, Australia; **Lewis Waber**, MD, PhD, Pediatric Genetics and Metabolism, University of Texas Southwest Medical Center, Dallas, TX; **Ray Pais**, MD, Pediatric Hematology/Oncology, East Tennessee Children's Hospital, Knoxville, TN

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