Direct Comparison of Measures of Endurance, Mobility, and Joint Function During Enzyme-Replacement Therapy of Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome): Results After 48 Weeks in a Phase 2 Open-Label Clinical Study of Recombinant Human N-Acetylglactosamine 4-Sulfatase

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ABSTRACT. Objective. Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disease caused by a deficiency of the enzyme N-acetylglactosamine 4-sulfatase (ASB). This enzyme deficiency leads to a progressive disorder with multiple tissue and organ involvement. The disease is rare and is heterogeneous in its clinical presentation and progression. A potential treatment for this disease exists in the form of enzyme-replacement therapy (ERT) with recombinant human ASB (rhASB), and a phase 1/2 randomized, double-blind, 2-dose (0.2 and 1 mg/kg) study in 6 patients showed the treatment at 48 weeks to be well tolerated. Greater biochemical efficacy based on a urine glycosaminoglycan occurred in the high-dose (1 mg/kg) group, and functional improvement seemed greater in patients in the high-dose group with rapidly advancing disease. On the basis of the phase 1/2 results, a phase 2, open-label study in patients with rapidly advancing disease was initiated primarily to evaluate efficacy variables that measure endurance, mobility, and joint function in a larger group of patients.

Methods. This was an open-label, multinational study of 10 MPS VI patients who received 48 weekly intravenous treatments with 1.0 mg/kg rhASB and had assessments of biochemical and clinical responses at regular intervals.

Results. After 24 weeks of treatment, each patient on average experienced a 155-m (98%) improvement in the 12-minute walk, a 64-m (62%) improvement at the 6-minute time point of the 12-minute walk, and a 48-stair (110%) gain in the 3-minute stair climb versus the baseline mean values. Additional improvements after 48 weeks of treatment were observed, including mean values of 211 m (138%) in the 12-minute walk, 75 m (80%) at the 6-minute time point of the 12-minute walk, and 61-stair (147%) gain in the 3-minute stair climb versus the baseline mean values. Joint Pain and Stiffness Questionnaire scores improved by at least 50% by week 24 and were maintained at week 48, whereas there were only small improvements in active shoulder range of motion (<10°) and in the time taken to stand, walk, and turn starting from a seated position (Expanded Timed Get-Up and Go test). Improvement in pulmonary function based on forced vital capacity and forced expiratory volume at 1 minute in the absence of growth was observed in 3 of 6 patients, and the observed gains occurred in the 24- to 48-week treatment interval. A mean decrease of 76% in urinary excretion of glycosaminoglycans indicated that a satisfactory biochemical response was achieved and the ERT was well tolerated.

Conclusions. The results suggest that a 12-minute walk extends the dynamic range of the conventional 6-minute walk and, along with the 3-minute stair climb, provide a robust approach to documenting the improvement in endurance in MPS VI patients who undergo ERT with rhASB. Pediatrics 2005;115:681–689. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1023; mucopolysaccharidosis VI, N-acetylglactosamine 4-sulfatase, enzyme-replacement therapy, glycosaminoglycans, clinical trial.

ABBREVIATIONS. MPS, mucopolysaccharidosis; ASB, N-acetylglactosamine 4-sulfatase; GAG, glycosaminoglycan; ERT, enzyme-replacement therapy; rhASB, recombinant N-acetylgalactosamine 4-sulfatase; ETGG, Expanded Timed Get-Up and Go; ROM, range of motion; FVC, forced vital capacity; FEV₁, forced expiratory volume at 1 minute; SpO₂, oxygen saturation by pulse oximeter; HAQ, Health Assessment Questionnaire; CHAQ, Childhood Health Assessment Questionnaire.

Mucopolysaccharidosis (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disease in which the affected individual lacks the enzyme N-acetylglactosamine 4-sulfatase (ASB), which hydrolyzes the sulfate moiety of the glycosaminoglycan (GAG) dermatan sulfate. In the absence of the enzyme, the stepwise degradation of dermatan sulfate is blocked, resulting in the intracellular accumulation of the substrate in the lysosomes of a wide range of tissues. The accumulation causes a progres-
sive disorder with multiple organ and tissue involvement that is variable in extent and timing. Affected infants seem normal at birth but will progress to advanced disease after a few years or over many decades depending on the extent of the enzyme deficiency. As with all the MPS disorders, MPS VI is a clinically heterogeneous disease in terms of the extent and rate of progression of organ impairment in affected individuals. Case studies reported in the literature have identified patients who presented with marked disease in the first year of life and those with slowly advancing disease that progressed over many decades. Typically, the most rapidly advancing form presents within the first several years of childhood with progressive degeneration of growth, skeletal deformities, coarse facial features, upper airway obstruction, recurrent airway and ear infections, and joint deformities. Ultimately, they become wheelchair bound or bedridden secondary to skeletal deformities, joint disease, cardiopulmonary disease, blindness, and spinal cord compression. It is uncommon for these patients to survive into their early 20s.

Treatment of MPS VI is limited to symptomatic care and bone marrow transplant. Although reports of the benefits of bone marrow transplant exist, the risk/benefit profile of the procedure has never been established in a randomized, controlled clinical study for this disease. One potential therapy that has been shown to be effective in animals and in human clinical studies is enzyme-replacement therapy (ERT). ERT has been approved for human use in the lysosomal storage disorders Gaucher disease, Fabry disease, and MPS I. Application of ERT with recombinant human ASB (rhASB) in a feline model for MPS VI disease demonstrated clearance of GAG from storage organs and improved joint mobility in juvenile affected cats and in prevention or slowing of skeletal dysplasia in affected cats that were treated from birth. These studies supported investigation of ERT in humans in a phase 1/2 randomized, double-blind, 2-dose (0.2 and 1 mg/kg) study in 6 patients with varying severity of MPS VI. Results reported for that study for the first 48 weeks of weekly infusions of rhASB showed the treatment to be well tolerated. Greater biochemical efficacy based on a more rapid and greater percentage reduction of urine GAG occurred in the high-dose (1 mg/kg) group, and functional improvement seemed greater in patients in the high-dose group with rapidly advancing disease. Six-minute walk test and shoulder range of motion (ROM) improved in all patients at 48 weeks, and joint pain improved in patients with pain at baseline. On the basis of these phase 1/2 results, the 1 mg/kg of rhASB was selected for a phase 2, open-label study in patients with rapidly advancing disease primarily to evaluate efficacy variables that measure endurance, mobility, and joint function in a larger group of patients.

METHODS

Study Design

This study was designed as an open-label, multicenter, multinational clinical study of the efficacy, safety, and pharmacokinetics of rhASB in patients with rapidly advancing MPS VI disease. Ten patients with MPS VI were enrolled at 1 of 2 sites. All patients had either biochemical or genetic proof supporting the MPS VI diagnosis. Patients were required during screening to walk unassisted at least 1 m but <250 m in 6 minutes. Patients were not allowed to walk unassisted for this inclusion criterion. Before baseline testing, each study patient participated in 2 consecutive phases, baseline phase (weeks 1–2) to assess eligibility and establish baseline parameters and a treatment phase (weeks 1–48). Within 2 weeks of completing the baseline phase, patients received an open-label intravenous administration of 1 mg/kg dose level of rhASB that continued during the treatment phase on a weekly basis (7 ± 3 days) for a minimum of 48 weeks. The study was conducted at 2 primary centers: 1 in the United States and 1 in Australia. After 6 weeks, patients were referred for treatment at a center close to their home once their local center received Institutional Review Board/Ethics Committee approval. Patients returned to their primary center at weeks 12, 24, and 48 for efficacy, safety, and pharmacokinetic measurements. The protocol was approved by the institutional review board at each participating clinical site. Written consent was obtained from all parents or guardians before enrollment, and written assent was obtained from all patients.

Study Drug

rhASB was produced in a suspension bioreactor by genetically engineered Chinese hamster ovary cells. The enzyme was purified through a traditional column chromatography procedure and formulated in phosphate-buffered saline (pH 5.8) that contained 0.085% polysorbate 80. The specific activity of the formulated enzyme averaged 56 units/mg. The purified enzyme contains a high level of bis-mannose-6-phosphate oligomannose oligosaccharide as confirmed by analytical assays and by the saturable robust “uptake” of enzyme by MPS VI fibroblasts in cell culture. Addition of 50 mM mannose-6-phosphate in the cell culture media reduced the fibroblast uptake by >90%.

rhASB Administration

Patients were premedicated with either diphenhydramine (0.5 mg/kg body weight) or promethazine (0.15 mg/kg body weight). rhASB was diluted in 0.9% saline and administered at 1.0 mg/kg over 4 hours once weekly. The infusion rate was adjusted so that ~2.5% of the total enzyme dose was infused during the first hour and the remaining enzyme dose (~97.5%) was infused over the next 3 hours.

Biochemical Studies

Studies to monitor toxicity were performed every 1 to 6 weeks and included complete blood count, chemistry panel, urinalysis, serum immunoglobulin G anti-rhASB antibody by enzyme-linked immunosorbent assay, and measurement of serum complement before and after infusion. Urine was obtained every 1 to 6 weeks to determine total GAG, a surrogate for the extent of clearance of these compounds from lysosomal storage. Total GAG concentrations in urine samples were determined with a method based on spectrophotometric detection of metachromatic changes to the dye 1,9-dimethylmethylen blue resulting from GAG binding. GAG concentrations were subsequently normalized to urinary creatinine concentrations, which were determined separately. Total GAG was quantified by measuring 1,9-dimethylmethylen blue binding, using dermatan sulfate as a standard. Pharmacokinetic studies were performed at 1, 2, 12, and 24 weeks. One-milliliter blood samples were collected from a second intravenous line placed in the arm opposite that used for the enzyme infusion. rhASB levels were measured by enzyme-linked immunosorbent assay.

Clinical Evaluations

Evaluation of mobility and physical function was performed at baseline and weeks 6, 12, 24, and 48. The 12-minute walk followed the guidelines for the 6-minute walk. Patients were instructed to walk unassisted as far as possible in 12 minutes but were allowed to rest when needed. The 3-minute stair climb was not a standardized test and was conceived on the basis of a combination of published tests and consideration of the physical limitations and safety of...
the population under study. Patients were instructed to climb as many steps as possible in a 3-minute period and were allowed to rest and use handrails during this test. The Expanded Timed Get-Up and Go (ETGG) test, originally designed to quantify functional mobility in the geriatric population, followed the published procedure.23 Each of these endurance tests was performed twice during assessment periods, and an average result was determined. Walk and stair-climb tests were performed on separate days.

ROM of the shoulders was measured with a goniometer by occupational and physical therapists.24,25 Forced vital capacity (FVC) and forced expiratory volume at 1 minute (FEV1) were evaluated by standard spirometry technique according to American Thoracic Society guidelines.26 Grip and pinch strength were measured with Martin Vigorimeter and B & L Engineering Pinch Gauge, respectively.27,28 Oxygenation during sleep was assessed on 2 separate nights by pulse oximetry continuous recording using Nellcor N-395 pulse oximeter. Assessments included average oxygen saturation by pulse oximeter (SpO2), lowest SpO2, total time the O2 saturation was <90%, and number of desaturations (oxygen saturation <85%) and/or drop of 4% below the baseline oxygen saturation for at least 10 seconds. Joint pain and stiffness from baseline and over the previous week were assessed by an analog scale based on the Health Assessment Questionnaire (HAQ)29,30 for patients who were >18 years old or Childhood Health Assessment Questionnaire (CHAQ)31 completed by the caregiver of patients who were ≤18 years old. Finally, each patient was videotaped while performing a standard set of physical movements based on activities in the Denver Developmental examination.18 Patients were asked to perform 5 tasks, each within a 3-minute period, including “put on shoes with hands,” “touch top of head with left hand,” “touch top of head with right hand,” “put on and take off sweatshirt,” and “pick up 10 coins and put them into a cup.”

An ophthalmologic evaluation that included fundoscopy and slit lamp examinations, assessment of glaucoma, and determination of visual acuity was performed at baseline and week 48. Standard 12-lead electrocardiogram was performed at baseline and at weeks 12, 24, and 48. Two-dimensional Doppler echocardiogram was completed at baseline and week 48. Liver and spleen volumes were calculated from the axial image data set using the Vision software, Raanana, Israel, and bone density was determined using QCT Pro (Mindways Software, San Francisco, CA).

Statistics

Descriptive statistics, including means, SDs, and percentage change over time, were calculated using Systat 10.2 (Systat Software, Inc, Richmond, CA). Change in parameter between baseline and at subsequent time points was compared using the paired t test. Pearson and Spearman correlations were determined for the 12-minute walk and stair climb using SAS version 8.2. Height and weight were compared with the National Center for Health Statistics reference data32 to determine age- and gender-specific z scores or SD scores using the NetScut anthropometry calculator.33 z scores were calculated as the difference between the observed value and the age- and gender-specific median value for the reference population divided by the SD of the reference population.34

RESULTS

Demographics

Ten patients who were between the ages of 6 and 22 years and had biochemical or genetic proof of the MPS VI diagnosis were selected on the basis of the inclusion criterion of a limitation in endurance based on a walk distance of <250 m at the 6-minute time point in a baseline 12-minute walk. Seven of the 10 patients exhibited the rapidly advancing form of the disease on the basis of the high degree of skeletal dysplasia and lysosomal storage (reflected in the high urinary GAG values) and short stature (mean height z score: -6.74) at baseline (Table 1).

Safety

All 10 patients completed 48 weeks of treatment with 475 of a possible 480 infusions completed. Seven serious adverse events were reported, with 6 judged unrelated and 1 possibly related to rhASB. The serious adverse event that was judged possibly to be related to study drug was an asthma attack that occurred after the infusion was completed in a patient with asthma that required continuous bronchodilators and oral and inhaled steroids. Subsequently, this patient was weaned off oral steroids by week 24. Twenty-nine drug-related adverse events occurred during the infusions, and these were primarily mild with 13 described as mild skin hypersensitivity noted in a single patient. No clinically significant abnormal hematologic, blood chemistry, or urinalysis findings were reported. Eight of the 10 patients developed antibodies within 6 weeks of treatment, but antibody levels did not correlate with adverse events or other safety measures (Fig 1). Depression in complement levels during infusion was noted in the 2 patients who developed the highest levels of antibodies.

TABLE 1. Baseline Patient Demographics

<table>
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<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Gender</th>
<th>Height, cm</th>
<th>Height z Score*</th>
<th>Weight, kg</th>
<th>Weight z Score*</th>
<th>Urine GAG, µg/mg Creatinine†</th>
<th>6-min Walk, m†</th>
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<td>-2.72</td>
<td>335.6</td>
<td>152.4</td>
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</table>

* Height and weight were compared with the National Center for Health Statistics reference data32 to determine age- and gender-specific z scores or SD scores using the NetScut anthropometry calculator.33 z scores were calculated as the difference between the observed value and the age- and gender-specific median value for the reference population divided by the SD of the reference population.34
† Normal values (mean ± SD) are age dependent: 3–12 years, 47.8 ± 11.6; 13–18 years, 22.7 ± 7.9; adult, 10.6 ± 3.2.
‡ Distance walked in the first 6 minutes of the 12-minute walk test (mean of 2 determinations on separate days).
§ Height and weight reference curves were only defined to 18 years. The patient calculated for a maximum age of 18 years.
Efficacy

Changes in urinary GAG concentration over the 48 weeks normalized to urinary creatinine concentration are presented in Fig 2. All patients showed large decreases in urinary GAG with 7 reaching levels $<100$ g/mg creatinine, with the remaining 3 between 100 and 200 g/mg creatinine. The 71% decrease at 24 weeks and 76% at 48 weeks are consistent with results obtained at the same dose in the phase 1/2 study.18

The results from the phase 1/2 MPS VI study suggested that increasing the time of the 6-minute walk would potentially extend the dynamic range of the test by capturing improvement in those patients who might improve after treatment by walking faster to those who might improve by walking much further at the same speed. The walk distance was increased to 12 minutes, with distances achieved at both the 6-minute and the 12-minute time points recorded. The results of these measures are presented in Table 2. A greater mean improvement was seen at the 12-minute time point, with each patient on average experiencing an improvement of 98% after 24 weeks and 138% after 48 weeks, versus the 6-minute time point with a per-patient improvement of 62% after 24 weeks and 80% after 48 weeks. The larger mean gains in the 12-minute versus 6-minute time point of the walk test were based on improvements in 1 patient who was unable to walk beyond 6 minutes at baseline and 2 additional patients who improved disproportionately in the distance that they walked in the second 6 minutes of the walk. Compared with baseline values, the results for both time points as a function of weeks of treatment were statistically highly significant (Table 2).

The stair climb has not been used as a measure of endurance for drug approvals, but it has been used historically as an integral part of preoperative assessment to gauge residual lung function in patients who undergo lung resection. There was variability in the number of stairs that patients could climb in 3 minutes at baseline, ranging from 20 to 92 stairs, but all patients showed an increase ranging from 3 to 115 stairs climbed in 3 minutes after 24 weeks, with continued improvement through 48 weeks (Table 2). The number of stairs climbed in 3 minutes increased significantly by an average of 110% (48 stairs) at week 24 and 147% (61 stairs) over the baseline at week 48. Compared with baseline values, the results as a function of weeks of treatment were statistically highly significant (Table 2). A strong linear relationship between the stair climb and the 12-minute walk was established on the basis of Pearson and Spearman correlations of 0.68 ($P = .03$) and 0.66 ($P = .038$), respectively.

The ETGG test was originally designed to quantify functional mobility in the geriatric population.23,35 The baseline mean of 31.33 ± 11.94 seconds in the present study is comparable to the mean time of 34.52 ± 10.62 seconds for an at-risk elderly population with histories of falls or gait and/or balance disorders and above that for normal young (15.36 ± 1.64 seconds) and health elderly (19.10 ± 2.11 seconds) individuals.23 For the patients in this study, there was a reduction of the mean total time between baseline, week 24, and week 48 from 31 to 26 to 23 seconds, respectively (week 24 vs baseline, $P = .002$; week 48 vs baseline, $P = .003$). Although the mean score did not fall into the normal range of the published values, 9 of 10 patients had a decrease in total time; in addition, the 1 patient who was unable to perform the test at baseline (completed only 10 m of the 20-m course) was able to complete the test in the
range of 29 to 35 seconds between the 24th and 48th weeks of treatment.

Pain and joint stiffness were measured at baseline and at weeks 6, 12, 24, and 48 using a modification of the CHAQ/HAQ questionnaires (Table 3). Pain and joint stiffness assessed for the previous week or relative to baseline were rated on a scale of 0 to 100, with 0 meaning no pain or joint stiffness and 100 meaning very severe pain or joint stiffness. At week 24 compared with baseline, pain decreased by a mean of 63 (41%) (P = .002) and stiffness decreased by 55 (24%) (P < .001). At week 48 compared with baseline, pain decreased on average by 55 (54%) (P = .015) and stiffness decreased by 63 (22%) (P < .001). These calculations are based on pain or joint-stiffness assessment. Active and passive shoulder flexion, extension, and lateral rotation were measured at baseline and at weeks 6, 12, 24, and 48. The mean improvement of any of these measurements was modest at <10° whether obtained by passive or active methods (data not shown). The latter results are consistent with the small change in the ratings of difficulty either as a mean or within a patient for the Quality of Life Measures. The task with the most improvement was the coin pick-up. At week 48, all 10 patients performed the task faster than at baseline (mean 17 ± 14 seconds faster; P = .004).

For the pinch test, 8 patients showed improvements, 6 of whom were at least 20% above baseline after 48 weeks of treatment. Compared with baseline, there was a mean 35 ± 33% increase at week 48 (P = .008). For the grip test, 7 patients had improvement in grip in both hands, 2 patients had declining scores after 48 weeks (after showing gains or no change for the first 24 weeks), and 1 patient failed to register a reading on the device during the entire study.

Appreciable gains (>10%) in FVC were observed in 5 patients, and these changes occurred primarily between 24 and 48 weeks of treatment (Table 4). The increase in FVC could be accounted for on the basis of changes in height in 2 patients. Reduction in liver and spleen size was observed in all 5 patients who presented with hepatosplenomegaly at baseline, and 4 of the 5 now have liver volumes in the normal
### TABLE 2.

<table>
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**DISCUSSION**

This phase 2 study of ERT for MPS VI was initiated to establish clinically meaningful measures of endurance, mobility, and joint function attributable to rhASB treatment. On the basis of the results of the previous phase 1/2 study, the inclusion criteria were modified in this phase 2 study to include a relatively uniform set of patients in regard to impaired endurance. Patients were required to walk <250 m in the first 6 minutes of a 12-minute walk at baseline. The results of the study indicated that a 12-minute walk provided a wider dynamic range in which to capture improvements in endurance relative to the 6-minute time point of the same walk. The 12-minute walk, 3-minute stair climb, and assessment of joint pain and stiffness by questionnaire offered the most clinically meaningful and sensitive measures of functional improvement that were established in as little as 24 weeks and continued to improve or were maintained over 48 weeks.

The walk test has been used primarily to measure cardiac or pulmonary disease and has been included as a primary outcome variable in clinical studies to measure treatment effects for pulmonary or cardiac disease. In other complex clinical situations, the walk test has been shown to be a measure of functional status, as shown recently for treatment of another mucopolysaccharidosis, MPS I. A clinically meaningful treatment effect was obtained in a 6-minute walk test in a placebo-controlled, double-blind study that assessed laronidase’s effectiveness for the treatment of MPS I, although statistical support for the 38.1-m difference between the treated and untreated groups was compromised by a wide baseline variability. However, this study did not use the distance walked before treatment as an inclusion criterion for enrollment, and only a single time (6 minutes) was used in the study. For the current MPS VI study, restricting the entry criterion and extending the walk to 12 minutes provided a larger treatment effect by allowing for an opportunity to capture both changes in speed for those who were capable of...
finishing the whole walking course and changes in
total distance for those who were incapable of walking
for 12 minutes at baseline. The variability at
baseline and during the treatment assessment inter-
vals was larger for the 12-minute versus the 6-minute
time points, a feature that is known from the litera-
ture. The improvements noted for the 6-minute
time point were superior to previously published
<40-m improvements in 6-minute-walk results for
the other drug treatments noted above.

The results of the present study suggest that the
stair climb is a supportive test for the 12-minute walk
because of the requirement to be able to have the
dexterity to step repeatedly down off the platform
without a handrail. The use of a stairway in a hos-
pital setting had the appeal of providing an appro-
riate handrail and floor surface.

The gains seen in pulmonary function in the ab-
sence of gains in height in this study were observed
in 3 of the 6 patients. Multiple pathologies contribute
to the profound restrictive disease, including abnor-
mal growth, morphology, and physical properties of
the skeletal system, poor muscle strength and struc-
ture, and stiff tendons and ligaments. To our knowl-
edge, no published reports have examined the mor-
phologic changes, mechanical properties, or diffusion
capacity of the lung parenchyma in MPS VI. Because
this disease is unique from other MPS disorders in
that the accumulated lysosomal product is solely
dermatan sulfate, it is impossible to draw analogies
relative to the changes observed for other MPS dis-
orders. As for the liver and spleen, several published
reviews list enlarged liver and spleen as a character-
istic of the disease. Preclinical studies in the MPS
VI–affected cat have documented that storage is con-
centrated primarily in the macrophages in these or-
gans, whereas in the MPS I dog, storage is present in

**TABLE 3.** Joint Pain and Stiffness Questionnaire

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline, Actual</th>
<th>Week 6</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (past week)</td>
<td>41</td>
<td>43</td>
<td>35</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Pain (past week vs baseline)</td>
<td>41</td>
<td>61</td>
<td>55</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>Joint stiffness (past week)</td>
<td>64</td>
<td>27</td>
<td>53</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>Joint stiffness (past week vs baseline)</td>
<td>64</td>
<td>24</td>
<td>46</td>
<td>56</td>
<td>62</td>
</tr>
</tbody>
</table>

Baseline pain scale: 0 to 100 (0 = no pain; 100 = very severe pain); baseline joint stiffness: 0 to 100 (0 = no joint stiffness; 100 = severe joint stiffness).

**TABLE 4.** Relationship of Height, FVC, Organomegaly, and Change in 12-Minute Walk Test and 3-Minute Stair Climb

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Baseline</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 48</th>
<th>Change in FVC*</th>
<th>Relative % ΔLiver Volume Week 48†</th>
<th>ΔSpleen Volume Week 48‡</th>
<th>Δ12-Minute Walk m, No. of Stairs (%)</th>
<th>ΔStair Climb, % Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>302</td>
<td>6</td>
<td>99.7</td>
<td>0.81</td>
<td>0.85</td>
<td>0.83</td>
<td>4.8 (4.8)</td>
<td>−13 −19.99</td>
<td>183.0 (42)</td>
<td>131.5 (198)</td>
<td>1.1 (0.8)</td>
</tr>
<tr>
<td>204</td>
<td>7</td>
<td>87</td>
<td>0.52</td>
<td>0.60</td>
<td>0.50</td>
<td>3.8 (4.4)</td>
<td>−4.5 −9.71</td>
<td>46.5 (10)</td>
<td>11.5 (13)</td>
<td></td>
</tr>
<tr>
<td>303</td>
<td>8</td>
<td>84.6</td>
<td>0.16</td>
<td>0.27</td>
<td>0.31</td>
<td>1.1 (1.3)</td>
<td>−13.6 −49.38</td>
<td>229.0 (227)</td>
<td>38.5 (179)</td>
<td></td>
</tr>
<tr>
<td>201</td>
<td>9</td>
<td>93.2</td>
<td>0.52</td>
<td>0.54</td>
<td>0.60</td>
<td>6.65 (7.1)</td>
<td>−14.4 −20.17</td>
<td>282.0 (111)</td>
<td>92.0 (460)</td>
<td></td>
</tr>
<tr>
<td>301</td>
<td>9</td>
<td>121.1</td>
<td>1.40</td>
<td>1.46</td>
<td>1.55</td>
<td>4.9 (4.0)</td>
<td>3 −2.56</td>
<td>120.0 (25)</td>
<td>115.1 (121)</td>
<td></td>
</tr>
<tr>
<td>203</td>
<td>15</td>
<td>107</td>
<td>0.28</td>
<td>0.27</td>
<td>0.38</td>
<td>1.9 (1.8)</td>
<td>−12.5 −20.22</td>
<td>120.0 (82)</td>
<td>22.5 (76)</td>
<td></td>
</tr>
<tr>
<td>304</td>
<td>16</td>
<td>124.7</td>
<td>0.83</td>
<td>0.74</td>
<td>0.83</td>
<td>1.3 (1.0)</td>
<td>−15.2 −6.03</td>
<td>595.0 (277)</td>
<td>135.5 (274)</td>
<td></td>
</tr>
<tr>
<td>202</td>
<td>17</td>
<td>120</td>
<td>0.75</td>
<td>ND</td>
<td>0.92</td>
<td>0.55 (&lt;1)</td>
<td>−5.3 −26.69</td>
<td>233.5 (57)</td>
<td>37.5 (48)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>18</td>
<td>96.2</td>
<td>0.47</td>
<td>0.44</td>
<td>0.48</td>
<td>−0.05 (&lt;1)</td>
<td>−15.2 −13.90</td>
<td>123.0 (378)</td>
<td>24.5 (102)</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>22</td>
<td>102.4</td>
<td>0.37</td>
<td>0.39</td>
<td>0.37</td>
<td>2.5 (2.4)</td>
<td>−20.9 −21.09</td>
<td>179.5 (179)</td>
<td>2.5 (9)</td>
<td></td>
</tr>
</tbody>
</table>

Δ indicates change.
* For patients 303, 201, 301, 203, and 202, the values indicate FVC values that represent an improvement from baseline of at least 10%.
† Mean liver size at baseline 681.6 ± 118 mL.
‡ Mean spleen size at baseline 146.8 ± 40 mL.
§ Liver volumes >95% limit were age-adjusted to body weight at baseline and week 48.
|| Liver volumes >95% limit were age-adjusted to body weight at baseline and within normal limits at week 48.
all cells. For the combined 16 patients who were treated in this study and the previous phase 1/2 study, only 4 had livers that were clearly enlarged, whereas another 2 had livers that were <10% larger than expected as a percentage of total body weight. It therefore is unlikely that gains in FVC are related to reductions in liver size in MPS VI.

The interpretation of pulmonary function tests in patients with MPS VI have several possible shortcomings on the basis of the information collected in the 2 ERT clinical studies completed. First, forced expiratory times have been consistently under 3 seconds. Second, the lung volumes being considered are extremely small (<1 L). The profound short stature and malformed skeletal system bring into doubt the value of determining the percentage predicted FVC value for this population as a way to gauge improvement. This situation is analogous to studies that have attempted to determine pulmonary function values in achondroplasia. Finally, improvements in such small lung volumes would be confounded by treatment-related straightening of joints producing variations of 1 to 2 cm in height.

Several new tests that may prove to be useful in the longer term were evaluated in this study. The rate of change of the improvements seen in the ETGG test suggests that additional reductions in the total time to complete the test are possible with longer follow-up. The use of a more appropriate grip bulb-based device (Martin Vigorimeter) in this study relative to the device used in the previous phase 1/2 study (Jamar Hand Dynamometer) has also yielded encouraging results. The modification of the CHAQ/HAQ to focus primarily on joint pain and stiffness yielded positive results and will be included in future studies. The attempt to differentiate the results relative to baseline versus the previous week was not achieved, so the need to compare with baseline is of no additional value. Although across-the-board improvements in the exploratory quality-of-life assessment were not achieved, modest improvement was observed for the coin pick-up test.

Several other measurements that were obtained in this study did not produce clinically meaningful improvements within the 48 weeks of treatment. Improvements were not expected in the echocardiogram and bone density assessments in this time frame on the basis of the phase 1/2 study. Improvement in visual acuity was also not achieved, but it would not be expected for enzyme to cross the retinal-blood barrier or reach the avascular cornea. The modest improvement of ≥10° in only 2 of 10 patients for active shoulder ROM is in contrast to the phase 1/2 study in which 3 of the 5 assessable patients at the 48-week time point achieved this level of improvement. One explanation may be that the degree of restriction at baseline was more significant in the phase 1/2 study. This is consistent with the finding of greater improvement in active shoulder ROM in the patients where baseline shoulder flexion was below the study median of 90.5° in the placebo-controlled, double-blind study for MPS I. In the phase 3 study, laronidase patients with that level of restriction had a mean improvement of 9.6°, whereas placebo patients had a mean decline of 4.8°.

The rapid improvement in the walk test, stair climb, and subjective sense of joint pain and stiffness suggest a physiologic basis of drug action that promotes more optimal joint function and well-being that goes beyond that of simple improvements in cardiorespiratory function. Longer term follow-up of the patients in this study and future controlled clinical studies of rHAASB are warranted to provide greater support for establishing this mechanism.

ACKNOWLEDGMENTS

This study was sponsored by BioMarin Pharmaceutical Inc and in part with funds provided by the National Center for Research Resources (5 M01 RR-01271 to P.H. and M01 RR00334 to R. Steiner), US Public Health Service.

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We acknowledge the participation of study patients and their families and the expert assistance of all study-site coordinators and study-site personnel.

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