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

Paul Harmatz, MD*; David Ketteridge, MBBS‡; Roberto Giugliani, MD, PhD§; Natalie Guffon, MD∥; Elisa Leão Teles, MD¶; M. Clara Sá Miranda, PhD#; Zi-Fan Yu, ScD**; Stuart J. Swiedler, MD, PhD†‡; and John J. Hopwood, PhD¶, for the MPS VI Study Group

ABSTRACT. Objective. Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disease caused by a deficiency of the enzyme N-acetylgalactosamine 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;e681–e689. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1023; mucopolysaccharidosis VI, N-acetylgalactosamine 4-sulfatase, enzyme-replacement therapy, glycosaminoglycans, clinical trial.

ABBREVIATIONS. MPS, mucopolysaccharidosis; ASB, N-acetylgalactosamine 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-acetylgalactosamine 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 deceleration 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 infants 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 deceleration 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 aware of this inclusion criterion before baseline testing. Each study participant participated in 2 consecutive phases, baseline phase (weeks 2 to 0) 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 0.05% 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-dimethylmethylene 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-dimethylmethylene 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. Distance walked at the 6- and 12-minute time points were recorded. The wall or handrails were allowed as guides only. The 3-minute stair climb is 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.2,23 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 Vigrometer 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 <89% 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.32 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 ophthalmology evaluation that included fundoscopic 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 and lumbar vertebral trabecular bone density (bone density completed only at the US site) were assessed by computed tomography scan at baseline and 48 weeks. The liver and spleen volumes were calculated from the axial image data set using the postprocessing graphic workstation (Picker Omnipro/Algotec Pro 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 hematology, 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). Depressions in complement levels during infusion was noted in the 2 patients who developed the highest levels of antibodies.

### Table 1: Baseline Patient Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Gender</th>
<th>Height, cm</th>
<th>Height z Score[^a]</th>
<th>Weight, kg</th>
<th>Weight z Score[^a]</th>
<th>Urine GAG, µg/mg Creatinine[^†]</th>
<th>6-min Walk, m[^‡]</th>
</tr>
</thead>
<tbody>
<tr>
<td>302</td>
<td>6</td>
<td>M</td>
<td>99.7</td>
<td>−3.37</td>
<td>18.6</td>
<td>−0.89</td>
<td>433.5</td>
<td>220.5</td>
</tr>
<tr>
<td>204</td>
<td>15</td>
<td>F</td>
<td>87.0</td>
<td>0.13</td>
<td>15.4</td>
<td>−2.34</td>
<td>510.5</td>
<td>246.5</td>
</tr>
<tr>
<td>303</td>
<td>20</td>
<td>F</td>
<td>84.6</td>
<td>−6.93</td>
<td>15.0</td>
<td>−2.83</td>
<td>360.6</td>
<td>85.0</td>
</tr>
<tr>
<td>201</td>
<td>9</td>
<td>M</td>
<td>93.2</td>
<td>−6.86</td>
<td>20.4</td>
<td>−2.04</td>
<td>342.0</td>
<td>137.5</td>
</tr>
<tr>
<td>301</td>
<td>9</td>
<td>M</td>
<td>121.1</td>
<td>−1.95</td>
<td>29.8</td>
<td>0.28</td>
<td>187.3</td>
<td>244.5</td>
</tr>
<tr>
<td>203</td>
<td>13</td>
<td>F</td>
<td>107.0</td>
<td>−8.12</td>
<td>29.6</td>
<td>−2.96</td>
<td>346.6</td>
<td>83.1</td>
</tr>
<tr>
<td>304</td>
<td>16</td>
<td>F</td>
<td>124.7</td>
<td>−5.66</td>
<td>29.0</td>
<td>−3.35</td>
<td>138.4</td>
<td>215.0</td>
</tr>
<tr>
<td>202</td>
<td>17</td>
<td>F</td>
<td>120.0</td>
<td>−6.80</td>
<td>32.6</td>
<td>−3.14</td>
<td>247.1</td>
<td>19.0</td>
</tr>
<tr>
<td>200</td>
<td>18</td>
<td>F</td>
<td>96.2</td>
<td>−11.32</td>
<td>20.4</td>
<td>−4.99</td>
<td>360.7</td>
<td>100.5</td>
</tr>
<tr>
<td>300</td>
<td>22</td>
<td>F</td>
<td>102.4</td>
<td>−10.28</td>
<td>21.0</td>
<td>−4.97</td>
<td>421.5</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.7</td>
<td>M</td>
<td>103.6</td>
<td>−6.74</td>
<td>23.2</td>
<td>−2.72</td>
<td>335.6</td>
<td>152.4</td>
</tr>
</tbody>
</table>

[^a]: Height and weight were compared with the National Center for Health Statistics reference data[^32] 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).

[^1]: 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 $<100 \text{µg/mg creatinine}$, with the remaining 3 between 100 and 200 $\text{µg/mg creatinine}$. 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 $\pm$ 11.94 seconds in the present study is comparable to the mean time of 34.52 $\pm$ 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 $\pm$ 1.64 seconds) and health elderly (19.10 $\pm$ 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\% (P = .002) and stiffness decreased by 55\% (P < .001). At week 48 compared with baseline, pain decreased on average by 55 \% (P = .015) and stiffness decreased by 63 \% (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: Endurance Parameters as a Function of rhASB Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48</th>
<th>Week 12-Baseline</th>
<th>Week 24-Baseline</th>
<th>Week 48-Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-min walk</td>
<td>N</td>
<td>Mean ± SD, m</td>
<td>Median</td>
<td>Minimum, maximum</td>
<td>Paired t statistic</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Absolute Distance Walked or Stairs Climbed Change Relative to Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-min walk</td>
<td>N</td>
<td>Mean ± SD, m</td>
<td>Median</td>
<td>Minimum, maximum</td>
<td>P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-min stair climb</td>
<td>N</td>
<td>Mean ± SD, m</td>
<td>Median</td>
<td>Minimum, maximum</td>
<td>P value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 intervals 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 given the significant correlation between the 2 tests. Bolton et al subjected 70 male subjects to a stair climb to determine the relationship between the number of steps climbed and the results of pulmonary function testing. These individuals were asked to walk up a maximum of 5 flights (127 stairs possible) without stopping, if possible. There was a strong relationship to pulmonary function tests, including FVC and FEV1, although the test was also an indicator of many other parameters, including cardiovascular status, cooperation, and determination. In a follow-up study of similar size, the number of stairs climbed correlated well with pulmonary function, although 61% of the performance on the stair climb could be explained by the aforementioned other parameters. Symptom-limited stair climbing has also been evaluated in individuals with chronic airflow obstruction. The group of 8 subjects with FEV1 < 0.9 L climbed only 61 ± 16 steps. Application of a symptom-limited stair climb in a clinical study for MPS VI presented several practical difficulties for this pediatric population, so the use of a timed interval was chosen instead. The step test, a variation of the stair climb, is a prime example of a similar test using a test interval of 3 minutes. Originally developed as a 2-step exercise test for adult cardiac assessment, a 3-minute step test was developed for cystic fibrosis. The use of the portable platform was judged to be problematic for the MPS VI population 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 hospital setting had the appeal of providing an appropriate handrail and floor surface.

The gains seen in pulmonary function in the absence of gains in height in this study were observed in 3 of the 6 patients. Multiple pathologies contribute to the profound restrictive disease, including abnormal growth, morphology, and physical properties of the skeletal system, poor muscle strength and structure, and stiff tendons and ligaments. To our knowledge, no published reports have examined the morphologic 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 disorders. As for the liver and spleen, several published reviews list enlarged liver and spleen as a characteristic of the disease. Preclinical studies in the MPS VI–affected cat have documented that storage is concentrated primarily in the macrophages in these organs, whereas in the MPS I dog, storage is present in

<table>
<thead>
<tr>
<th>TABLE 3. Joint Pain and Stiffness Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Baseline, Actual</td>
</tr>
<tr>
<td>% Improvement</td>
</tr>
<tr>
<td>Patient Age, y</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>Baseline FVC, L</td>
</tr>
<tr>
<td>Week 24 FVC*</td>
</tr>
<tr>
<td>Week 48 FVC*</td>
</tr>
<tr>
<td>Change in Height, cm (%)</td>
</tr>
<tr>
<td>Relative %</td>
</tr>
<tr>
<td>ΔLiver Volume Week 48†</td>
</tr>
<tr>
<td>ΔSpleen Volume Week 48‡</td>
</tr>
<tr>
<td>Δ12-Minute Walk, m No. of Stairs (%)</td>
</tr>
<tr>
<td>302 6 99.7 0.81 0.85 0.83 4.8 (4.8) −13 −19.99 183.0 (42) 131.5 (198)</td>
</tr>
<tr>
<td>204 7 87 0.52 0.60 0.50 3.8 (4.4) −4.5 −9.71 46.5 (10) 11.5 (13)</td>
</tr>
<tr>
<td>303 8 84.6 0.16 0.27 0.31 1.1 (1.3) −13.8 −49.38 229.0 (227) 38.5 (179)</td>
</tr>
<tr>
<td>201 9 93.2 0.52 0.54 0.60 6.65 (7.1) −14.4 −20.17 282.0 (111) 92.0 (460)</td>
</tr>
<tr>
<td>301 9 121.1 1.40 1.46 1.55 4.9 (4.0) 3 2.56 120.0 (25) 111.5 (121)</td>
</tr>
<tr>
<td>203 15 107 0.28 0.27 0.38 1.9 (1.8) −12.5 −20.22 120.0 (82) 22.5 (76)</td>
</tr>
<tr>
<td>304 16 124.7 0.83 0.74 0.83 1.3 (1.0) −15.2 −6.03 595.0 (277) 135.5 (274)</td>
</tr>
<tr>
<td>202 17 120 0.75 ND 0.92 0.35 (&lt;1) −5.3 −26.69 233.5 (57) 37.5 (48)</td>
</tr>
<tr>
<td>200 18 96.2 0.47 0.44 0.48 (0.05 (&lt;1) −15.2) −13.90 123.0 (378) 24.5 (102)</td>
</tr>
<tr>
<td>300 22 102.4 0.37 0.39 0.37 2.5 (2.4) −20.1 −21.09 179.5 (179) 2.5 (9)</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.
controlled, double-blind study for MPS I. In the
the patients where baseline shoulder flexion was
phase 1/2 study. This is consistent with the finding
improvement. One explanation may be that the degree
of ROM is in contrast to the phase 1/2
nal-blood barrier or reach the avascular cornea. The
would not be expected for enzyme to cross the reti-
frame on the basis of the phase 1/2 study.18 Improve-
gram and bone density assessments in this time
provements within the 48 weeks of treatment. Im-
no additional value. Although across-the-board im-
ments. 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 im-
provements 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. Im-
provements were not expected in the echocardi-
gram and bone density assessments in this time
frame on the basis of the phase 1/2 study.18 Improv-
ment in visual acuity was also not achieved, but it
would not be expected for enzyme to cross the reti-
nal-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, iduronidase patients with that level of
restriction had a mean improvement of 9.6°, whereas
placebo patients had a mean decline of 4.8°.12

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 pro-
motes 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 clin-
ic studies of rhASB 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 (S M01 RR-01271 to P.H. and M01 RR00334 to R.
Steiner), US Public Health Service.

MPS VI Study Group co-authors: Robert Steiner, MD (Division of
Metabolism, Oregon Health and Science University, Portland,
OR); Ida Schwartz, MD, and Ana Cecilia Azevedo, MD (Servicio de
Genética Médica, Hospitales de Clínicas de Porto Alegre, Porto
Alegre, Brazil); Bonito Victor, MD (Unidade de Doencas Metabóli-
cas, Departamento Pediatria, Hospital de Sao Joao, Porto, Portugal);
Laura Keppen, MD (Department of Pediatrics, University of South
Dakota School of Medicine, Sioux Falls, SD); David Sillence, MD
(Children's Hospital, Westmead, Australia); Lionel Lubitz, MD
(Royal Children's Hospital, Melbourne, Australia); William
Frischman, MD (Townsville Hospital, Townsville, Australia); John
Waterson, MD, PhD, and Julie Simon, RN (Children's Hospital &
Research Center, Oakland, CA); and Stephanie Oates, RN (Depart-
ment of Genetic Medicine, Women's and Children's Hospital Ad-
elaide, North Adelaide, Australia).

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

REFERENCES

1. Neufeld EF, Muenzer J. The mucopolysaccharidosis. In: Scrivé C, Beau-
det AL, Valle D, Sly WS, eds. The Metabolic Basis of Inherited Disease. New
2. Spranger JW, Koch F, McKusick VA, Natzschka J, Wiedemann HR,
Zellweger H. Mucopolysaccharidosis VI (Maroteaux-Lamy’s disease).
Heritable Disorders of Connective Tissue. 5th ed. St Louis, MO: CV Mosby;
4. Fong LV, Menahem S, Wraith JE, Chow CW. Endocardial fibroelastosis
infantile cardiomyopathy as a presenting feature of mucopolysacchari-
6. Pizl H, von Figura K, Goebel HH. Deficiency of arylsulfatase B in 2
brothers aged 40 and 38 years (Maroteaux-Lamy syndrome type B).
7. Tonnissen T, Gregersen BN, Guttler F. Normal MPS excretion, but
dermatan sulphuria, combined with a mild Maroteaux-Lamy pheno-
marrow transplantation for lysosomal storage diseases. The European
10. Krivit W. Maroteaux-Lamy Syndrome (mucopolysaccharidosis type
VI). Treatment by allogeneic bone marrow transplantation in 6 subjects
and potential for autotransplantation bone marrow gene insertion. Int
mucopolysaccharidosis I: a randomized, double-blinded, placebo-
controlled, multinational study of recombinant human alpha-L-
Direct Comparison of Measures of Endurance, Mobility, and Joint Function During Enzyme-Replacement Therapy of Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome): Results After 48 Weeks in a Phase 2 Open-Label Clinical Study of Recombinant Human N-Acetylgalactosamine 4-Sulfatase
Paul Harmatz, David Ketteridge, Roberto Giugliani, Natalie Guffon, Elisa Leão Teles, M. Clara Sá Miranda, Zi-Fan Yu, Stuart J. Swiedler and John J. Hopwood

_Pediatrics_ 2005;115;e681
DOI: 10.1542/peds.2004-1023

Updated Information & Services
including high resolution figures, can be found at:
/content/115/6/e681.full.html

References
This article cites 40 articles, 7 of which can be accessed free at:
/content/115/6/e681.full.html#ref-list-1

Citations
This article has been cited by 5 HighWire-hosted articles:
/content/115/6/e681.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
**Rheumatology/Musculoskeletal Disorders**
/cgi/collection/rheumatology:musculoskeletal_disorders_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2005 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.
Direct Comparison of Measures of Endurance, Mobility, and Joint Function During Enzyme-Replacement Therapy of Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome): Results After 48 Weeks in a Phase 2 Open-Label Clinical Study of Recombinant Human \( N \)-Acetylgalactosamine 4-Sulfatase

Paul Harmatz, David Ketteridge, Roberto Giugliani, Natalie Guffon, Elisa Leão Teles, M. Clara Sá Miranda, Zi-Fan Yu, Stuart J. Swiedler and John J. Hopwood

*Pediatrics* 2005;115:e681

DOI: 10.1542/peds.2004-1023

The online version of this article, along with updated information and services, is located on the World Wide Web at:

/content/115/6/e681.full.html