ENZYME REPLACEMENT THERAPY FOR MUCOPOLYSACCHARIDOSIS VI: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTINATIONAL STUDY OF RECOMBINANT HUMAN N-ACETYLGALACTOSAMINE 4-SULFATASE (RECOMBINANT HUMAN ARYLSULFATASE B OR RHASB) AND FOLLOW-ON, OPEN-LABEL EXTENSION STUDY

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and STEVEN J. SNAEDLER, MD, PhD, for the MPS VI Phase 3 Study Group.

Objective The objective of this Phase 3 study was to confirm the efficacy and safety of recombinant human arylsulfatase B (rhASB) treatment of mucopolysaccharidosis type VI (MPS VI; Maroteaux-Lamy syndrome), a rare, fatal lysosomal storage disease with no effective treatment.

Study design Thirty-nine patients with MPS VI were evaluated in a randomized, double-blind, placebo-controlled, multicenter, multinational study for 24 weeks. The primary efficacy variable was the distance walked in a 12-minute walk test (12MWT), whereas the secondary efficacy variables were the number of stairs climbed in a 3-minute stair climb (3MSC) and the level of urinary glycosaminoglycan (GAG) excretion. All patients received drug in an open-label extension period for an additional 24 weeks.

Results After 24 weeks, patients receiving rhASB walked on average 92 meters (m) more in the 12MWT (p = .025) and 5.7 stairs per minute more 3MSC (p = .053) than patients receiving placebo. Continued improvement was observed during the extension study. Urinary GAG declined by -227 ± 18 μg/mg more with rhASB than placebo (p < .001). Infusions were generally safe and well tolerated. Patients exposed to drug experienced positive clinical benefit despite the presence of antibody to the protein.

Conclusion rhASB significantly improves endurance, reduces GAG, and has an acceptable safety profile. (J Pediatr 2006;148:533-9)

Mucopolysaccharidosis type VI (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disease in which deficient activity of the enzyme N-acetylgalactosamine 4-sulfatase (aryl sulfatase B, or ASB; E.C # 3.1.6.12) impairs the stepwise degradation of the glycosaminoglycan (GAG) dermatan sulfate. Partially degraded GAG accumulates intracellularly in lysosomes causing a chronic progressive disorder resulting in death in the second or third decade. Aside from symptomatic treatment, MPS VI has no satisfactory specific therapy. Some patients have benefited from bone marrow transplantation.

A survey of 121 MPS VI-affected persons showed the wide variation in clinical
However, high urinary GAG values (>200 μg/mg creatinine) were associated with an advanced clinical course relative to age characterized by short stature, low body weight, impaired endurance based on a walk test, compromised pulmonary function, and reduced joint range of motion (ROM). Both physical endurance and urinary GAG values appear to be important parameters to assess treatment options.

Two clinical studies for enzyme replacement therapy (ERT) using recombinant human ASB (rhASB) have been reported. In a Phase 1/2 study, weekly infusions of 1 mg/kg rhASB were shown to be well tolerated, produce a rapid reduction in urinary GAG levels, and improve endurance in patients with rapidly advancing disease. A Phase 2 study also showed a rapid improvement in endurance based on a 12-minute walk test (12MWT) and 3-minute stair climb (3MSC). These promising results led to a Phase 3 study designed to evaluate the efficacy and safety of rhASB.

METHODS

Study Design

This was a randomized, double-blind, multicenter, placebo-controlled, 24-week Phase 3 study of rhASB followed by a 24-week extension period. Following screening eligibility assessments, eligible patients completed baseline assessments, and they were randomized in a 1:1 ratio to receive weekly intravenous infusions of either rhASB 1.0 mg/kg or placebo solution for 24 consecutive weeks. After 24 weeks, all patients completing treatment were enrolled in the open-label extension. The investigator and staff supervised infusions, but they did not participate in the efficacy assessments and were not informed of the original treatment assignments of their patients until all patients completed the Week 48 assessment. An Institutional Review Board or Ethics Committee at each participating clinical site approved the protocol. All adult patients and parent/guardians gave written consent; patients <18 years of age gave written assent according to local Institutional Review Board regulations.

Patient Selection

Patients with MPS VI (n = 39) were enrolled at six clinical sites. Inclusion criteria specified that patients be at least 7 years of age and have either biochemical or genetic proof supporting the MPS VI diagnosis. Patients were required during screening to walk unaided at least 5 m and no more than 270 m in the first 6 minutes, or no more than 400 m total in 12 minutes, in a 12MWT. Key exclusion criteria included clinically significant spinal cord compression, or a medical condition or other extenuating circumstance that could interfere with study compliance.

Study Drug

rhASB was produced in a perfusion bioreactor by genetically engineered Chinese hamster ovary cells, purified by conventional column chromatography, and formulated in phosphate buffered saline at pH 5.8 containing 0.005% Polysorbate 80. The specific activity of the formulated enzyme, based on hydrolysis of 4-methylumbelliferyl sulfate, was 60 to 80 units/mg representing >99% purity with >99% conversion of the unmodified (inactive) cysteine residue to formylglycine (active) in the active site of the enzyme based on peptide mapping.

Study Drug Administration

Patients were premedicated with either diphenhydramine 0.5 mg/kg body weight or promethazine 0.15 mg/kg body weight. rhASB (1 mg/kg) or placebo solution was diluted with 250 mL of sterile 0.9% saline and administered over 4 hours once weekly with 2.5% of the total dose infused during the first hour and the remainder over the next 3 hours.

Efficacy Evaluation

The primary efficacy endpoint variable, the distance walked in a 12MWT, provided a measure of endurance. Assessments were completed twice (on separate days) at baseline, and at Weeks 6, 12, 18, 24, 36, and 48 following published American Thoracic Society guidelines for the 6MWT that had been previously used for the 12 MWT in the Phase 2 study. Secondary efficacy endpoints included the 3MSC and urine GAG. The 3MSC followed procedures previously used in the Phase 2 study. To measure GAG, urine was obtained as the first morning void before study drug infusion. Total GAG concentration was determined with a validated method.

Tertiary end points included: (1) assessments of joint pain, joint stiffness, and physical energy level; (2) assessment of joint ROM; and (3) assessment of hand dexterity as evidenced by number of coins picked up in 1 minute.

Several clinical parameters were evaluated to provide additional evidence of the severity of disease before treatment and to allow long-term evaluation of rhASB treatment. Respiratory function was evaluated using standard pulmonary function tests that followed American Thoracic Society guidelines. Cardiac function was evaluated by echocardiography. Health resource utilization was assessed, and patients underwent ophthalmologic evaluations.

Safety Evaluation

Safety was assessed by evaluation of medical history, completion of physical examinations, measurement of vital signs, recording of adverse events (AEs), serial assessment of immunologic parameters (IgG anti-rhASB antibody and complement levels), monitoring of changes in laboratory parameters (chemistry, hematology, urinalysis, thyroid function), and assessment of electrocardiography. AEs that occurred during infusion and were judged to be possibly, probably, or definitely related to study drug were considered infusion-associated reactions (IARs).
Statistical methods

Patients were randomized to either the rhASB or placebo group, stratified by primary site of treatment and blocked within site. The efficacy analyses included all randomized patients; safety analyses included all patients who received at least one dose of study drug. For the blinded portion of the study, a prospectively defined longitudinal analysis compared rhASB with placebo with respect to the primary outcome variable, meters walked in 12 minutes, where (a) the method was a repeated measures linear model with two covariates, baseline walk distance and site; (b) the time of measurement entered the model in a way that did not force a linear trend over time (ie, formally entered as a categorical variable); (c) the model used a compound symmetry covariance structure; and (d) the model included a time by treatment interaction.

The open-label extension examined trends over time separately for each group. The patterns of each treatment thus were examined by two separate longitudinal models—one for the group originally given rhASB (rhASB/rhASB) and one for the placebo group now receiving drug (placebo/rhASB). The models, similar to the form described earlier, include all time points from baseline to Week 48 in the response, with the following comparisons: (a) Week 24 change from baseline; (b) Week 48 change from baseline; and (c) Week 48 change from Week 24. A prespecified supportive analysis analyzed the first 6 minutes of the 12MWT in the same manner as done for the primary analysis.

Similar analyses were performed for the 3MSC and most of the tertiary efficacy outcome variables. The prespecified analysis for the 3MSC stated that the rate of climb, defined by the (number of stairs climbed) / (number of minutes in the climb), would serve as the outcome variable if >10% of all of the assessments exceeded the entire staircase in <3 minutes. Because 17% of all stair climbs reached the top of the staircase in the first 24 weeks, the endpoint variable was the rate of stair climb. An analysis of variance of Week 24 urinary GAG levels was used to compare the rhASB and placebo groups. The model was stratified by site and used baseline urinary GAG level as a continuous covariate. For shoulder joint ROM, the primary endpoint was a binary variable: improvement by at least 10 degrees ROM analyzed using a Mantel-Haenszel test, stratified by site. For respiratory function, an analysis of variance model was employed with treatment group, baseline measurement, and site as covariates.

Computation for all results was performed using the Statistical Analysis Systems (SAS®) Version 8.2 (SAS Institute Inc., Cary, NC). All statistical tests were conducted at a two-sided type I error rate of 0.05. All P values reported are two-sided unless otherwise noted. P values <.05 (two-sided) were considered statistically significant.

RESULTS

Characteristics of Patients

Characteristics of the study patients are shown in Table I. Although those in the placebo group were, on average, younger, shorter, and weighed less than those in the rhASB group, none of these differences was statistically significant. All 28 eligible patients were randomized, as were 11 patients who did not fulfill inclusion criteria. Seven of these exceeded the walk distance eligibility entry criteria at screening, 3 were <7 years of age, and 1 had experienced a failed bone marrow transplant 11 years earlier.

<table>
<thead>
<tr>
<th>Table I. Baseline characteristics</th>
<th>rhASB (N = 19)</th>
<th>Placebo (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td>12 (63)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>MALE</td>
<td>7 (37)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>AGE (YEARS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEAN (SD)</td>
<td>13.7 (4.67)</td>
<td>10.7 (4.35)</td>
</tr>
<tr>
<td>MINIMUM, MAXIMUM</td>
<td>8, 29</td>
<td>5, 20</td>
</tr>
<tr>
<td>MEDIAN</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>25TH AND 75TH PERCENTILES</td>
<td>8, 17</td>
<td>8, 12</td>
</tr>
<tr>
<td>RACE, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHITE</td>
<td>16 (84)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>BLACK</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>ASIAN</td>
<td>1 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>AMERICAN INDIAN</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>HEIGHT (CM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STANDING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEAN (SD)</td>
<td>104.4 (12.87)</td>
<td>100.3 (13.54)</td>
</tr>
<tr>
<td>MINIMUM, MAXIMUM</td>
<td>90, 136</td>
<td>81, 140</td>
</tr>
<tr>
<td>WEIGHT (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEAN (SD)</td>
<td>24.6 (9.14)</td>
<td>20.8 (7.85)</td>
</tr>
<tr>
<td>MINIMUM, MAXIMUM</td>
<td>14, 47</td>
<td>14, 46</td>
</tr>
</tbody>
</table>

Primary Efficacy Variable: 12MWT

Table II 4 summarizes the primary and secondary variables, statistical tests, and key results for the blinded portion of the study. For the 12MWT, the observed mean ± SD walk distance for the rhASB group at baseline was 227 ± 170 m and for the placebo group was 381 ± 202 m; this difference was statistically significant (P = .014). The rhASB group greatly improved their walk distance during the first 6 weeks of treatment, with continued, steady improvement that leveled off after Week 18 (Figure 1). The difference between the two groups estimated under the longitudinal model was 92 ± 40 m at Week 24 (P = .025) with a 95% confidence limit of (11 m, 172 m) (Table II). In support of this difference, the rhASB group increased their distance walked at the 6-minute timepoint of the 12MWT by 53 m at Week 24 compared with no change in the placebo group (P = .007).

Initiation of the placebo group on rhASB produced a steady increase in the 12MWT distance between Week 25 and Week 48 (Figure 1; Table III, available at www.jpeds.com). The rhASB/placebo group experienced a continued improvement in walk distance (Figure 1 and Table III).
Table II. Summary of effect on primary and secondary endpoints for the 24-week double-blind study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statistical method</th>
<th>Estimated difference rhASB group and placebo group at 24 weeks</th>
<th>95% confidence limit</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Variable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12MWT</td>
<td>Longitudinal analysis</td>
<td>92 m mean improvement in favor of rhASB</td>
<td>(11, 172)</td>
<td>.025</td>
</tr>
<tr>
<td>6MWT (supportive of primary)</td>
<td>Longitudinal analysis</td>
<td>53 m mean improvement in favor of rhASB</td>
<td>(14, 90)</td>
<td>.007</td>
</tr>
<tr>
<td><strong>Secondary Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3MSC: rate</td>
<td>Longitudinal analysis</td>
<td>5.7 stairs/min mean improvement in favor of rhASB</td>
<td>(-0.1, 11.5)</td>
<td>.053</td>
</tr>
<tr>
<td>3MSC: number of steps (supportive of 3MSC rate)</td>
<td>Longitudinal analysis</td>
<td>16.3 ± 7 mean improvement in favor of rhASB</td>
<td>(0.62, 31.9)</td>
<td>.042</td>
</tr>
<tr>
<td>Urinary GAG levels</td>
<td>Analysis of variance</td>
<td>-227 µg/mg creatinine mean decrease in favor of rhASB</td>
<td>(-265 µg/mg, -190 µg/mg)</td>
<td>.001</td>
</tr>
<tr>
<td># of responders with baseline</td>
<td>Fisher’s exact test; exact inversion of two one-sided intervals for confidence intervals</td>
<td># of responders: 17/19 in rhASB group, 0/19 in the placebo group</td>
<td>Difference in proportions: (0.67, 0.99)</td>
<td>.001</td>
</tr>
<tr>
<td>GAG reduced ≥ 50% (supportive of GAG levels)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Secondary Endpoints: 3MSC and Urinary GAG Level**

The results of the 3MSC were consistent with those of the 12MWT (Figure 2). The mean difference in the change in the 3MSC rates of the rhASB and placebo patients at Week 24 was 5.7 ± 2.9 stairs/min (p = .053; Table II). Initiation of the placebo group on rhASB produced an increase in stair climb rate (p = .001; Table IV, available at www.jpeds.com). The rhASB/rhASB group experienced continued improvement (Table IV).

The change from baseline to Week 24 in the 12MWT was highly correlated with change in the rate of the 3MSC.

The correlation between the two changes was 0.69 (p = .001) in the rhASB group and 0.45 in the placebo group (p = .051).

Baseline urinary GAG levels were similar in the two groups (Figure 3). In the rhASB group, the mean level of 346 ± 128 µg/mg creatinine decreased rapidly to a mean of 85 ± 36 µg/mg creatinine at Week 24, a 75% reduction from baseline. Adjusted for baseline, the analysis of variance showed an estimated mean difference at Week 24 between placebo and rhASB groups of -227 ± 18 µg/mg creatinine (p < .001) with a 95% confidence limit of (-265, -190 µg/mg).

![Figure 1. 12MWT vs treatment week. The fitted means from the longitudinal model for the change from baseline in the distance walked in 12 minutes for the rhASB group (filled circles) and placebo group (open circles) were estimated for each treatment week. The dotted line at Week 24 denotes the last timepoint of the double-blind study after which all patients received weekly infusions of rhASB.](image1)

![Figure 2. 3MSC vs treatment week. The fitted means from the longitudinal model for the change from baseline in the rate of stairs climbed per minute in 3 minutes for the rhASB group (filled circles) and placebo group (open circles) were estimated for each treatment week. The dotted line at Week 24 denotes the last timepoint of the double-blind study after which all patients received weekly infusions of rhASB.](image2)
creatinine; Table II). Once initiated on treatment with rhASB, the placebo/rhASB group experienced a similar reduction in mean urinary GAG levels between Week 25 and 48 (Figure 3).

**Respiratory Function**

Several parameters of respiratory function were assessed as long-term measures of efficacy. As in the two previous studies, forced vital capacity (FVC) (Table V, available at www.jpeds.com) and forced expiratory volume in 1 second (FEV₁, data not shown) did not improve in the present study. The respiratory parameter, maximum voluntary ventilation (MVV), was defined prospectively to capture improvement in rib-cage excursion as a result of increased strength or flexibility. Improvement in MVV in the rhASB/rhASB group was observed over the 48-week period, and in the placebo/rhASB group between Week 24 and 48. The sample size was small, the variability large, and the gains not statistically significant (Table V).

**Tertiary End Points**

Treatment with rhASB did not appear to have an effect on any of the other tertiary endpoint variables during the 24-week randomized phase or the 24-week open-label extension (data not shown).

**Safety**

All but one patient completed 48 weeks of study; one patient withdrew from the study after four infusions of placebo for reasons unrelated to treatment. Compliance with infusions was high, with 1801 of 1841 infusions completed (98%). The incidence of total AEs, severe AEs, and serious AEs was similar in the two groups (Table VI, available at www.jpeds.com) consistent with most AEs being a result of pre-existing medical problems. The majority of IARs during weeks 1–24 (56/60 or 93.3%) were mild to moderate in nature (Table VII, available at www.jpeds.com) and responded to interruption or slowing of the infusion rate, or administration of additional antihistamines or antipyretics. Corticosteroids were administered to 5 of the 38 patients before or during infusion in response to IARs, accounting for 60 of the 1345 (4.5%) rhASB infusions received weeks 1–48.

During the 48 weeks of the study, two serious AEs occurred that the investigators judged as related to the study drug. One patient in the rhASB/rhASB group experienced apnea that resulted in emergency placement of a tracheotomy. This patient tolerated all other infusions suggesting that the apnea was most likely related to the diphenhydramine premedication and the patient’s poor respiratory status. A patient in the placebo/rhASB group experienced respiratory distress with shortness of breath and an oxygen saturation of <89% on room air. The incident was successfully managed by stopping the infusion and administering oxygen and albuterol.

All but 1 of the 38 patients developed IgG antibody to rhASB as assessed by enzyme-linked immunosorbent assay after 24 weeks of rhASB treatment. IARs were more common in patients with the highest relative antibody levels, although the frequency and timing of these events did not necessarily correspond to the first report of antibody positivity or the time of maximum antibody titer for the majority of patients. The relationship of antibody levels to urinary GAG levels showed that most patients had low antibody levels and low urinary GAG levels after 24 weeks (filled and open circles in Figure 4; available at www.jpeds.com). At 48 weeks, all but 6 patients in the rhASB/rhASB group (denoted in filled squares in Figure 4) maintained low antibody and urinary GAG levels. For 5 of these, the levels of antibodies and GAGs continued to rise between Weeks 25 and 48 (denoted by the arrows in Figure 4), although all maintained a comparable reduction (65%) in urinary GAG relative to the cohort. The 43% reduction in the sixth patient indicated partial impairment of enzyme uptake or activity; this was confirmed pharmacokinetically by low levels of circulating enzyme and the presence of neutralizing antibodies in serum samples (data not shown).

Few clinically significant changes occurred in vital signs, clinical chemistry, hematology, or urinalysis results over the 48-week study period; those that did occur were single events.

**DISCUSSION**

Mucopolysaccharidosis VI is a rare, fatal lysosomal storage disease with no effective treatment. Administration of 1.0 mg/kg rhASB led to a statistically significant improvement in endurance, as measured by the 12MWT and 5MSC; and in a statistically significant decline in urinary GAG excretion. rhASB was well tolerated, with most AEs attributable to manifestations of the MPS VI disease. IARs related to study drug administration were readily managed and did not result in discontinuation of the study drug or in serious sequelae for any patient. Finally, the improvements in efficacy...
and safety were confirmed in the follow-on 24-week open-label extension period.

The improvement in endurance demonstrated by the results of the 12MWT was both statistically significant (p = .025) and clinically meaningful (92 m). Although a formal 6MWT was not performed in the rhASB Phase 3 study, the mean difference between the treated and placebo groups at the 6-minute timepoint of the 12MWT was 53 meters (p = .007). This result was comparable or superior to the relative treatment effect observed for the 6MWT for the approved drug for MPS I\(^{10}\) or pulmonary hypertension.\(^{11}\) The distance walked in 6 minutes is recognized as a strong independent predictor of morbidity and mortality in patients with congestive heart failure\(^{12,13}\) and with primary pulmonary hypertension.\(^{14}\) An observed difference of 54 m (95% CI, 37 to 71 m) has been estimated as the minimal clinically significant improvement in elderly with chronic obstructive pulmonary disease.\(^{15}\) The 3MSC, a measure of endurance utilized in the Phase 2 study,\(^{6}\) supported the results of the 12MWT. Bolton and colleagues showed that the number of stairs climbed correlated well with pulmonary function, although 61% of the performance on the stair climb could be explained by cardiovascular status, cooperation, and determination.\(^{16,17}\)

Urinary GAG excretion is associated with a reduction in lysosomal storage in well-vascularized tissues as observed during rhASB treatment of feline MPS VI.\(^{18,19}\) The reduction in urinary GAGs levels observed in the Phase 3 study was similar to the reductions observed in the two previous studies.\(^{5,6}\) The tight clustering of absolute urinary GAG levels after treatment relative to a 5- to 10-fold range of baseline levels suggests that the 1 mg/kg dose provides a sufficient pharmacodynamic response across the entire disease spectrum.

The improvements in MVV suggest an improvement in rib-cage excursion as a result of improved strength or flexibility. These changes constituted improved respiratory mechanics rather than improvement in pulmonary function. Potential mechanisms include improvement in upper airway obstruction, improvement in thoracic skeletal mechanics and/or improved respiratory muscle effort.

Improvement in the tertiary end-point variables was observed independent of treatment in almost all of these measures. Although reported gains in similar measures were reported in the previous two studies\(^{5,6}\) the Phase 1/2 study had small groups (n = 3) and the Phase 2 study did not include a placebo group. Patients in the Phase 3 study were also not selected on the basis of their baseline values for these variables or had low levels of impairment. Access to better medical care may also have contributed to the improved outcomes, as documented with gains in joint ROM in a treatment study for MPS I.\(^{20}\)

Infusions with rhASB were well tolerated. The majority of the patients experiencing IARs did have high levels of IgG antibody, although there were many exceptions. The nature of the IARs (eg, urticaria, rash, rigors, conjunctivitis, dyspnea, chest pain, and abdominal pain) and their recurrence in the rhASB group are consistent with immune reactions expected with infused recombinant proteins. Five patients in this group had recurrent infusion reactions during the first 24 weeks of rhASB treatment, but only three continued to have reactions during Weeks 25 to 48, whereas two had no further reactions. Four additional patients (two from rhASB group, two from the placebo group) started experiencing these reactions during Weeks 25 to 48. The reactions were manageable; they responded to interruption of the infusion and adjustment of the rate of the infusion as well as to the administration of supplemental antihistamines and anti-inflammatory agents such as ibuprofen and corticosteroids.

All but one of the patients in the study developed IgG antibody to rhASB after 24 weeks of drug infusion. Despite the presence of antibody to the protein, patients exposed to drug still experienced positive clinical benefit, although this antibody appeared to partially interfere with the reduction in urinary GAG excretion in at least one patient. Although not dictating any specific treatment in these patients, routine follow-up of antibody levels, urinary GAG values, and urine protein will insure that there is no long-lasting negative impact in these persons.

In conclusion, the results presented for 48 weeks of this Phase 3 study confirm the effectiveness of weekly administration of 1.0 mg/kg rhASB on endurance and urinary GAG excretion and demonstrate a favorable safety profile for this compound in patients with MPS VI.


REFERENCES

8. Whitley CB, Ridnour MD, Draper KA, Dutton CM, Neglia JP.


