# CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**125117/0**

## MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

**Division of Therapeutic Biologic Internal Medicine Products**
**HFD-108**

**Date:** **May 27, 2005**

**From:** **John Hyde, Ph.D., M.D., Clinical Team Leader, DTBIMP** John E Hyde 5-27-05

**Through:** **Marc Walton, M.D., Division Director, DTBIMP**

**Subject:** **Supervisory Summary Review of BLA/STN 125117/0**
**Galsulfase for Mucopolysaccharidosis Type VI (Maroteaux-Lamy Syndrome)**

**To:** **BLA 125117/0 File** 5-31-05
**Karen Weiss, M.D.; Director, ODE 6**

## Identifying information

| | |
|---|---|
| BLA/STN#: | 125117 |
| Applicant: | BioMarin |
| Biologic name: | Galsulfase |
| Proposed trade name: | Naglazyme |
| Submission date: | November 23, 2004 |
| Stamp date: | November 29, 2004 |
| PDUFA goal date: | May 31, 2005 |
| Formulation: | 5 mg galsulfase (expressed as protein content) in 5 mL sterile solution, single use vials for injection |
| Proposed indication: | Treatment of Mucopolysaccharidosis Type VI to improve endurance as evidenced by an increase in walking and stair-climbing capacity. |
| Proposed regimen: | 1 mg/kg intravenous infusion every week |

**Recommended regulatory action**: Approval under 21 CFR 601

## Introduction and Regulatory Background

This BLA is for the new molecular entity Naglazyme (galsulfase), an exogenous source of enzyme intended to treat severe deficiency of *N*-acetylgalactosamine 4-sufatase, the defect causing Mucopolysaccharidosis Type VI (MPS VI, also known as Maroteaux-Lamy syndrome).

The enzyme, produced by recombinant DNA technology, is one of the normal variants of the human enzyme. The product is to be administered weekly at a dose of 1 mg/kg as an intravenous infusion over four hours. The product is proposed as a treatment for MPS VI to improve walking and stair-climbing capacity.

Orphan Designation 98-1198 was granted for this product on February 17, 1999, "for the treatment of mucopolysaccharidosis Type VI." Clinical studies of galsulfase were conducted under BioMarin's BB-IND 9057, which was received on May 2, 2000. Fast Track Designation was granted to BioMarin on June 26, 2000, for the investigation of galsulfase for "its effect in decreasing the incidence of cardiac or respiratory failure in patients with mucopolysaccharidosis VI." An End-of Phase-2 Meeting was held July 22, 2003. A pre-BLA meeting was held on September 28, 2004, and the BLA submission was received on November 29, 2004. Although the clinical studies in the application did not address the objectives of the Fast Track designation, the application was granted Priority review status because it was viewed as representing, if approved, a significant improvement over currently available therapies.

No Advisory Committee meeting was convened to discuss this application. However, an Endocrinologic and Metabolic Drugs Advisory Committee meeting was held on January 15, 2003, to discuss the application for Aldurazyme (laronidase) for treatment of Mucopolysaccharidosis Type I. The disease, treatment approach, and clinical evaluation for that application had important similarities to those for this application. The deliberations and recommendations of that committee meeting have direct relevance to the present application, as discussed below.

The primary review disciplines have all written review documents, which should be consulted for more specific details of the application. This memorandum summarizes selected information from these documents. The primary review documents relied upon are the following:

Clinical efficacy and safety review of J. Irony, with contribution by A. Pariser
Statistical review of J. Derr
Clinical pharmacology review of A. Rajpal
Pre-clinical pharmacology and toxicology review of W. Gao
Product review of S. Beaucage
Immunogenicity assays review of R. Bernstein
Study site inspection memo of J. Tavarez
Facility memorandum of J. Li and C. Renshaw
DMETS consultation of L. Pincock (including DDMAC recommendation)

## Clinical Background

Mucopolysaccharidosis Type VI (MPS VI, or Maroteaux-Lamy syndrome) is a lysosomal storage disease, a category of diseases is characterized by a genetic deficiency in production or function of one or more the lysosomal enzymes. In MPS VI, the deficient enzyme is N-acetylgalactosamine 4-sulfatase (also known as Arylsulfatase B, or ASB), which removes sulfate esters from chondroitin 4-sulfate and dermatan sulfate. Dermatan sulfate accumulates in lysosomes in cells throughout the body and causes injury to multiple organ systems. While there

are normal variants of the enzyme, several genetic mutations have been identified that cause clinical disease. Enzyme activity of at least 5% appears necessary to avoid disease. In the patients studied in the Phase 3 study for this application, the activity averaged less that 1% of the lower limit of normal.

In the classic form of MPS VI, the diagnosis is made between 6 and 24 months. The physical manifestations are growth deceleration, coarse facial features, skeletal and joint deformities, upper airway obstruction, heart valve disease, and hydrocephalus secondary to meningeal involvement, but mental development is usually normal. Death usually comes in the second decade as a result of respiratory infection or heart disease. Milder forms of the disease may present with short stature, corneal clouding, osteonecrosis of the hips, and aortic stenosis. Survival in milder cases is possible into the fourth decade. Urinary glycosaminoglycan (GAG) levels in MPS VI patients are elevated to several times the normal levels.

There is no approved specific treatment for the disease. The currently available therapeutic options are primarily symptomatic and palliative. Bone marrow transplantation has been used to benefit in a few patients, but the morbidity and mortality have led to its use being reserved for rapidly progressive forms in young children. There is a pressing need for new therapies.

The disorder is extremely rare. It is estimated that there are about 1100 cases worldwide, with prevalence in the U.S. thought to be between 50 and 300 cases. The 56 patients who participated in the clinical trials for this application thus may comprise approximately 5% of the world population of MPS VI patients.

## Chemistry, manufacturing, and controls issues

The reader is referred to the Product review by S. Beaucage.

Galsulfase is produced by recombinant DNA technology in a Chinese hamster ovary cell line. [redacted]. The commercial drug substance is manufactured by BioMarin at their Galli facility in Novato, CA, using a [redacted]. The final manufacturing takes place at [redacted], with release testing performed by BioMarin (or at a U.K. site for E.U. distribution). The final product consists of 5 mg galsulfase in 5 mL sterile solution in a stoppered glass vial.

The initial clinical study used a formulation that did not include polysorbate 80. It was deemed comparable to the polysorbate 80 formulation by a PK study. The clinical material used in the Phase 2 and Phase 3 clinical studies differed from the commercial material in that the drug substance was produced using a [redacted]. The clinical material was judged comparable to the commercial scale material and bioequivalence was established in a PK study.

Real-time studies are underway to support an expiration dating of [redacted], but currently available data support stability only through 30 months.

The manufacturing facilities were found to be in compliance with cGMPs and capable of manufacturing Naglazyme in a consistent manner using validated processes.

BioMarin has developed assays for IgG anti-product antibody, IgE anti-product antibody, neutralizing antibody, and galsulfase. None has had adequate validation. The IgG anti-product antibody assay was used on samples from almost all of the patients in the clinical studies. Of the 54 patients evaluated, 98% developed antibodies. Antibody titers did not appear to bear any relationship to incidence or severity of infusion reactions, and the significance of the antibody titers remains unclear. The IgE assay was used on only 2 patients' samples, and the neutralizing antibody was used in only one case: a patient had a high IgG (binding) antibody titer and appeared to have a somewhat reduced urinary GAG response. The neutralizing antibody assay was positive, but subsequent GAG response did not worsen despite progressively rising binding antibody levels. The significance of a positive neutralizing antibody finding is unclear.

Conclusions and Recommendations
The product reviewer recommended that the product is approvable with a 30-month expiration date. He also recommended that the "do not freeze" directions remain in the labeling as BioMarin originally proposed.

The product reviewer negotiated post-marketing commitments to use additional substance and product release specifications, to add substance and product release tests, to re-evaluate substance and product specifications, and to evaluate alternative methods and enhancements for assays used in production.

The immunogenicity reviewer concluded that none of the clinical assays has adequate validation. He recommended post-marketing commitments to develop and validate the IgG and IgE binding antibody assays, the neutralizing antibody assays, and the assay for galsulfase, and to apply the antibody assays to banked specimens from the Phase 3 study.

## Pre-clinical pharmacology and toxicology issues

The reader is referred to the Pre-clinical Pharmacology and Toxicology review by W. Gao.

From *in vitro* studies using human fibroblasts from subjects with MPS VI, it was found that galsulfase was taken up by cells, transported to lysosomes, and rapidly produced clearance of dermatan sulfate.

The effects of galsulfase were evaluated in several studies using a feline model of MPS VI. Urinary glycosaminoglycan (GAG) levels were significantly reduced compared to untreated animals, but still remained above normal. In tissues obtained 2 days after an infusion, complete elimination of GAG was seen in the liver and spleen reticuloendothelial cells and renal interstitial cells, but no effects were seen on aortic smooth muscle, heart value fibroblasts, or chondrocytes. Enzyme activity was found in several tissues, with levels being highest in the liver, but no activity was seen in articular cartilage, skin fibroblasts, or cornea. In the studies of MPS VI kittens treated from birth, skeletal changes appeared milder than in untreated disease,

but were not normalized. In older cats no affect on skeletal structure was noted. In a study using intra-articular injection in the feline model, skeletal changes were not normalized, but those treated with combined intra-articular and systemic therapy had improved joint shape and larger epiphyses. The galsulfase-injected joints showed less distention of articular chondrocytes than non-injected joints, but there was no change in cartilage thickness. Of interest, the four cats who received combined therapy did not develop antibodies.

Toxicology evaluation in cats found slight or moderate elevations in alkaline phosphatase and ALT, and mild pneumonitis and glomerulonephritis were observed in some studies. Most cats developed antibodies. In cynomolgus monkeys there was mild bile duct hyperplasia and chronic periportal inflammation at doses over 3 mg/kg/week and mild adrenal cortical atrophy at 10 mg/kg/week (an exposure estimated to be comparable to 21 to 32 times the human dose). Minimal to moderate serocellular/pustular epidermatitis occurred at all dose levels in several females. One monkey died without abnormal clinical signs, and a cause of death was not determined. All monkeys developed antibodies. Transient swelling of face or paws was seen in rats at a single dose of 10 mg/kg. There were no significant toxicological findings in Beagle dogs up to a dose of 20 mg/kg.

Reproductive and developmental toxicity studies were conducted at doses up to 3 mg/kg/day in rats. No effects were seen on fertility, reproduction, or fetal development.

No gentoxicity or carcinogenicity studies were conducted.

Conclusions and Recommendations

The pre-clinical reviewer concluded that the product was approvable, that the pregnancy category should be B, and that the mutagenesis and fertility section of the labeling should refer to the animal studies by dose given rather than as a multiple of human dose due to the difference in regimens.

The reviewer also recommended that reproductive toxicity should be evaluated in a non-rodent model as a post-marketing commitment. The sponsor committed to conducting a [redacted] and a definitive developmental toxicity study in a non-rodent species.

## Clinical Pharmacology Issues

The reader is referred to the Clinical Pharmacology review by A. Rajpal.

In the Phase 1/2 and Phase 2 studies blood galsulfase concentrations fell rapidly after the end of the infusions, with an elimination half-life after the initial dose of 4 to 19 minutes. For the second and subsequent doses the clearance dropped by a factor of about a half compared to the initial dose, and the AUC values approximately doubled. Pharmacokinetic parameters remained relatively constant through 96 weeks. The patient with the highest antibody levels showed a fall in AUC from Week 1 to Week 24, contrasting sharply with the rises seen in all other patients; two other patients with relatively high antibody levels did not have unusual values for AUC. The reviewer speculated that very high antibody levels might be interfering in the galsulfase assay, but the interpretation of the finding is unclear.

A subset of patients who received Naglazyme in the Phase 3 study had pharmacokinetic measurements, and these formed the basis for the pharmacokinetic parameters in the labeling. They were reasonably consistent with parameters estimated from the earlier studies, except that the mean clearance did not change appreciably from Week 1 to Week 24. The reviewer proposed that the table present medians, which better reflected the overall PK findings.

Urinary GAG concentration was used as a pharmacodynamic endpoint. Most patients showed a decrease of 70% to 80% of baseline values by the fourth week of treatment, but average values remained somewhat above the normal range. Mean urinary GAG levels stayed relatively constant after that time, in the face of antibody levels that tended to rise on average through Week 24, although one patient in the Phase 3 study developed high antibody levels that appeared to be neutralizing. The patient also had the highest urinary GAG levels at Week 24 with only a 44% reduction compared to baseline.

The clinical study material used substance from a — process, whereas the commercial material uses a — process. Patients in the Phase 1/2 and Phase 2 studies participated in a PK/PD comparability study. The lots were deemed comparable based on $C_{max}$, $AUC_{0-t}$ (AUC from start of infusion until 1 hour after the end of the infusion), and urinary GAG, although the $AUC_{0-\infty}$ had an upper confidence limit of 130%.

There were no special drug-drug interaction studies. There were no studies of pharmacokinetics in special populations.

Conclusions and Recommendations

The Clinical Pharmacology reviewer drew the following conclusions:

- Pharmacokinetics were not linear between 0.2 and 1 mg/kg/week, as the AUC increased much more than 5-fold.
- Pharmacokinetics using the proposed dose appear independent of duration of therapy beginning with the second dose through 194 weeks.
- In the Phase 3 study, clearance and $V_Z$ were related to antibody level at Week 24 in patients with titer ≥ 10 OD, but it is unclear if that represented an effect on pharmacokinetics or the assay.
- There were no apparent trends in pharmacokinetic parameters as a function of age or gender, but the number of patients was small.
- The clinical and commercial process materials are comparable with regard to pharmacokinetics.

The reviewer recommended labeling changes to provide medians and ranges of pharmacokinetic parameters rather than means and standard deviations, and to expand the discussion of the association between high antibody levels and pharmacokinetic changes. Refer the review for specific details of the proposed labeling changes.

## Clinical/Statistical Issues

The reader is referred to the Clinical review by I. Irony, with contribution by A. Pariser, and to the Statistical review by J. Derr.

### Phase 1/2 and Phase 2 Studies

The seven-patient Phase 1/2 study involved a randomized, double-blind comparison of galsulfase 0.2 mg/kg vs. 1 mg/kg given weekly for 24 weeks. It included efficacy, safety, and PK/PD assessments. The change in six-minute walk distance from baseline to Week 24 averaged 42 meters in the 1 mg/kg group. Each patient's urinary GAG fell to less than half of the baseline value for both doses. In an extension, patients were treated with 1 mg/kg weekly, and four have continued to receive treatment through the time of submission. The effect on urinary GAG has persisted through 144 weeks. Of six patients who were evaluated, all developed antibodies.

The ten-patient Phase 2 study collected open-label efficacy, safety, and PK/PD data. Patients were treated with Naglazyme 1 mg/kg weekly for 48 weeks, and most patients have continued to receive Naglazyme in an extension study. The 12-minute walk test improvement averaged 155 meters at Week 12, and 211 meters by Week 48. There was no evidence for improvement in specific measures of respiratory or joint function. Urinary GAG averaged less than half of baseline levels at four weeks, and averaged near, but still above, the upper limit of normal at 72 weeks. All patients developed antibodies.

### Phase 3 study

The sole Phase 3 study was a randomized, double-blind comparison of Naglazyme 1 mg/kg vs. placebo weekly for 24 weeks to evaluate safety and effects of treatment on tests of physical performance. It also included PK/PD assessments and a variety of tertiary efficacy measurements. To be eligible, patients were required to have a diagnosis of MPS VI with clinical signs and symptoms and enzyme activity less than 10% of the lower limit of normal, and they were required to be able to walk between 5 and 270 meters in the first six minutes of a 12-minute walk test.

Patients were randomized with equal probability to Naglazyme or placebo, blocked and stratified by center. Treatment was given every week intravenously over four hours. All patients were premedicated with antihistamines. Details of the infusion could be modified if the patient had infusions reactions (see the clinical review for specific information).

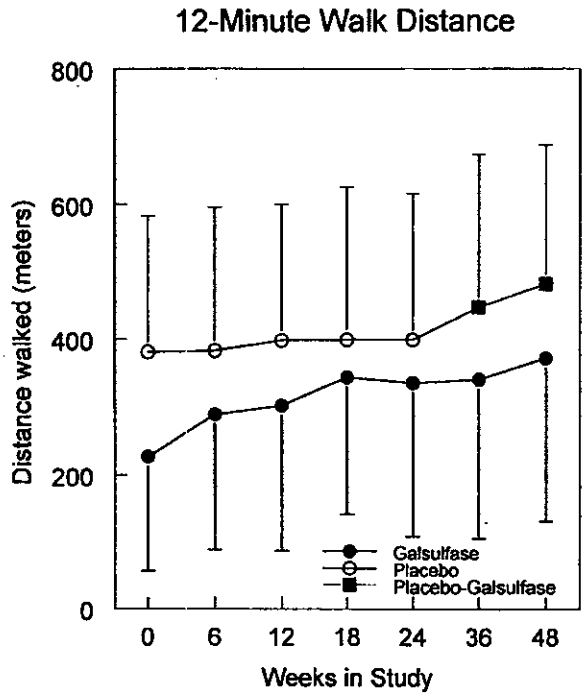
The primary endpoint was distance walked on a 12-minute walk test (12-MWT), which was administered at baseline and every six weeks through Week 24. The test was conducted using standardized equipment and protocol. The outcome at a given visit was defined as the average of two distances walked from two tests done a few days apart. The statistical analysis plan specified a repeated measures analysis of the change from baseline to Week 24 in distance walked, stratified by center and adjusted for baseline distance walked.

At the conclusion of the study placebo patients were switched to Naglazyme, but patients remained blinded to initial treatment and additional efficacy measurements were made through week 48. Patients have continued receiving Naglazyme through an open-label extension study.

A total of 39 patients participated at six sites in six different countries. There were 19 patients randomized to Naglazyme and 20 randomized to placebo, however one placebo patient withdrew consent and stopped participating before the first post-baseline walk test. Subjects in the two treatment groups were similar at baseline in many respects, although the Naglazyme group averaged 3 years older (13.7 vs. 10.7 years) and was slightly taller (104 vs. 100 cm). Manifestations of diseases were very similar and enzyme activity averaged 0.7% of lower limit of normal in both groups. The most striking difference however, was a substantial imbalance in the baseline primary endpoint, distance walked on the 12-MWT: the average (± SD) was 227 (± 120) meters for Naglazyme vs. 381 (± 202) meters for placebo. This outcome complicates interpretation of the primary analysis, as will be discussed below.

With the exception of the placebo patient who dropped out, and one patient who missed testing at Week 18, collection of the primary endpoint data was complete. One walk test result was dropped for one subject: on blinded review of cases with discrepancies between the first and second 12-MWT at each assessment point, one subject was identified who did markedly worse on the second trial due to an acute illness. Only the (better) value from the first walk test was used. This subject received Naglazyme. Dr. Irony reviewed case report forms for all cases of discrepancies between first and second walk test results. He concurred that the deletion of the second walk test was reasonable for this patient, and that no other cases were identified where a similar adjustment of the data would have been be warranted. There were protocol violations regarding limit on baseline walk distance, as several patients who walked too far on screening were nonetheless allowed into the study.

The raw means and standard deviations for the 12-MWT at each assessment point are shown in the graph and table below (adapted from the clinical review):




Distance Walked in 12 MWT

| Timepoint | Galsulfase | | Placebo | | Difference (Mean ± SE) |
|---|---|---|---|---|---|
| | N | Mean ± SD (meters) | n | Mean ± SD (meters) | |
| Baseline | 19 | 227 ± 170 | 20 | 381 ± 202 | -154 ± 60 |
| Week 6 | 19 | 290 ± 201 | 19 | 383 ± 213 | - 93 ± 67 |
| Week 12 | 19 | 303 ± 216 | 19 | 398 ± 208 | - 94 ± 69 |
| Week 18 | 18 | 344 ± 202 | 19 | 399 ± 226 | - 55± 70 |
| Week 24 | 19 | 336 ± 227 | 19 | 399 ± 217 | - 63± 72 |
| Week 36 | 18 | 341 ± 235 | 18 | 447 ± 227 | * |
| Week 48 | 18 | 372 ± 240 | 18 | 482 ± 206 | * |

*At week 36 and 48 all subjects were treated with galsulfase in an open label manner.

This table demonstrates the baseline imbalance in distance walked. Even with the greater improvement in distance walked in the Naglazyme group, the mean distance walked at 24 weeks was still less in the Naglazyme group than in the placebo group. Analysis of the difference from baseline shows that the mean improvement on Naglazyme was 83 meters more than on placebo. Using the primary analyses model incorporating repeated measures analysis, site effect, and adjustment for baseline distance walked, the estimated difference in improvement is 92 meters, which is statistically significant with p = 0.025, two-sided.

Because the case for efficacy rests heavily on this one small study, the results were scrutinized carefully. Items that were given particular attention were as follows:

Adjustment for baseline imbalance: Baseline distance walked was lower in the Naglazyme group, so that mean distance walked was still lower at Week 24 despite a greater increase from baseline. Because adjustment for baseline distance is critical to the analysis, the appropriateness of the adjustment was examined. Despite the large difference in means, there was substantial overlap of the distributions of baseline distance walked. Although there was a slight tendency for shorter distance walked at baseline to be associated with greater improvements by Week 24, the trend was not particularly strong, corresponding to the fact that the adjustment only changed the estimated effect by 9 meters. Further, the linear trends were reasonably similar in the two groups, supporting the assumptions underlying the adjustment procedure.

Although the analysis of the effect of baseline on outcome is intended to take regression to the mean into account, additional data were available to address the point. Most of the patients in the Phase 3 study had participated in BioMarin's natural history study, and walk test results that had been done months or more before study entry were available from most patients. Dr. Irony compared the baseline walk test results to the earlier results to see if there was any tendency for the Naglazyme group to have had atypically poor performance at study entry compared to the earlier result. No clear underperformance at baseline was identified. This analysis showing no clear trend in walk test performance over time also gave some affirmation to the finding of only a small improvement the 12-MWT for the placebo group in the controlled study.

If patients with relatively high performance on the walk test have little room for improvement compared to poor performers (a "ceiling effect"), the baseline imbalance could favor the group with poorer initial performance. This concern is reasonably addressed by the observation of the increased walk distances in the placebo group after they had crossed over to Naglazyme at Week 24. The mean increase for the 18 placebo subjects was 66 meters (one dropped out after the crossover, so this is not the same as the difference in means in the table above). That was somewhat less that the improvement over the initial 24 weeks in the initial Naglazyme group, but it does suggest that there was no strong ceiling effect, as well as lending support to the estimate of the size of the treatment effect.

Susceptibility to unblinding: The 12-MWT is effort dependent, and so could be susceptible to bias by patients' expectations if there is significant unblinding. All patients were given antihistamines prior to infusion, which could reduce infusion reactions as well as provide some sense of drug effect for placebo patients. Infusion reactions were not very frequent, and it also turned out that a substantial fraction of placebo patients had at least one infusion reaction. Analysis of response according to who had an infusion reaction did suggest some effect, but within each stratum, the effect of Naglazyme appeared similar to the overall effect. Among the four best responders in the Naglazyme group, two had no infusion reaction, and one had mild shivering once after the Week 18

visit and walked only 3.5% farther at the next and final visit. The fourth had a syncopal reaction with the first infusion but no subsequent infusion reactions

Other sensitivity analyses: Additional sensitivity analyses were performed by the sponsor and by the statistical review; refer to Dr. Derr's review for details. These included alternative models for analysis as well as examination of different patient subsets, including those who had not violated walk test entry criteria. These analyses generally support the estimated magnitude of treatment effect and strength of evidence. Dr. Derr also reviewed the treatment allocation procedures and found them to be adequate.

The dataset for the pivotal study was small, so that ability to look at any special subpopulations is severely limited. The relatively even gender distribution did make analysis by sex feasible. It appeared that the treatment effect was mainly observed in the female subset, similar to a phenomenon that was seen in the clinical trial of Aldurazyme (laronidase) for MPS I.

An important secondary endpoint was rate of stair climbing in a 3-minute stair climb test. The correlations between 12-MWT and stair climbing improvement had values for $R^2$ generally slightly less than 0.5, leading one to expect some redundancy from this assessment but also suggesting that stair climbing may have captured some independent component of the treatment effect. The results paralleled those for the 12-MWT: there was baseline imbalance, a greater improvement in the Naglazyme-treated group, and a comparable improvement in the placebo group after they were switched to Naglazyme. The statistical test of the difference in improvement over the control period had a p-value of 0.053.

The clinical sties in Oakland, CA, Mainz, Germany, and Manchester England were inspected. The inspections noted some protocol deviations in eligibility criteria, some failures to use proper methods for collecting tertiary endpoints, and a potential for unblinding from analysis of blood samples for complement activation in some cases. The findings were not considered to be so serious as to make the data from the sites unacceptable for use in support of the BLA.

## Safety

The reader is referred to Dr. Irony's review for full details of the safety analysis. The safety database from placebo-controlled trials included 55 patients exposed to some formulation of galsulfase; all but a few of those were exposed to the recommended regimen of Naglazyme. The extent of exposure as of the safety update is shown below:

Numbers of Patients Exposed to Galsulfase
as of Safety Update

| Exposure | Patients Receiving Any Dose | Patients Receiving 1 mg/kg |
|---|---|---|
| Any | 55 | 53 |
| > 3months | 54 | 53 |
| > 6 months | 54 | 53 |
| > 9 months | 53 | 53 |
| > 1 year | 34 | 34 |
| > 1.5 years | 15 | 15 |
| > 2 years | 5 | 3 |
| > 3 years | 3 | 3 |

There was one death in a 15 year old patient who withdrew from the Phase 1/2 study after three weeks of treatment. He had brain glioma and colon cancer diagnosed at ten and 14 months, respectively, after entering the study. He was found to have a germline mutation in a DNA mismatch repair gene. The possibility of a role for Naglazyme in the patient's death appears remote.

Identification of drug-related toxicity is challenging because MPS VI patients have significant underlying morbidity so that serious adverse events would not be unexpected in the course of a 24-week study, and the systematic collection of adverse events in a placebo comparison group was limited to essentially 19 patients for 24 weeks. Dr. Irony reviewed reports of non-fatal serious adverse events and performed additional, treatment-blinded categorization analyses of all adverse events reported in the clinical studies, pooling events in related groups to increase the sensitivity of the analysis.

The principal finding was a higher rate of infusion reactions associated with Naglazyme, some severe, a finding that could be expected based on experience with other therapeutic proteins. Fever, chills, headache, rash, and mild urticaria were the common presentations. The less common but severe reactions included angioneurotic edema, hypotension, dyspnea, bronchospasm, respiratory distress, apnea and urticaria. Slower infusions, sometimes with additional medications, were usually sufficient to manage the reactions, and no patient had to discontinue the course of therapy. No cases of classic anaphylaxis were identified, but the infusion reactions were of sufficient significance that a warning is appropriate.

Using an unvalidated IgG binding antibody assay, 98% of patients tested developed antibodies, but antibody titer bore no clear relationship to treatment response or adverse events. Neutralizing antibodies were found in one patient who was tested, but the meaning of the result was unclear.

The size of the clinical study patient population is severely limited by the rarity of the disease. With a sample of 55 patients, an adverse event would need to affect 5.5% of the MPS VI population in order to have a 95% probability of having being seen. This limitation underscores the importance of asking BioMarin to conduct a port-marketing registry study for systematic collection of additional safety data.

Conclusions and Recommendations
The clinical reviewer concluded that the application provided adequate evidence of efficacy and an acceptable safety profile and was approvable. The reviewer recommend post-marketing commitments to conduct a long-term registry study, including experience in patients younger that 5 years, and to

In negotiations with BioMarin, the company committed to conducting the registry study, obtaining additional experience at the recommended dose in patients under 5 years, and to

The clinical team found these commitments adequate.

## Advisory Committee

This application was not presented to an Advisory Committee. On January 15, 2003, the Endocrinologic and Metabolic Drugs Advisory Committee held a discussion of the application for Aldurazyme (laronidase), an exogenous enzyme therapy for Mucopolysaccharidosis Type I that was approved on April 30, 2003. There are many similarities between the applications for Naglazyme and Aldurazyme regarding the nature of the disease, the approach to therapy, and the clinical studies.

For the Aldurazyme submission, the principal clinical data came from a six-month, placebo-controlled study. Urinary GAG was markedly reduced but not normalized. There was a statistically significant difference (p=.03) for the modest increase of 4.5 percent predicted in forced vital capacity (FVC) and difference in a six-minute walk test of 38 meters (p=.066, or p=0.4 with adjustment for baseline imbalance). The Committee felt that, given the challenges in study the disease, a six-month study was not ideal but of adequate duration. They unanimously considered the clinical evidence for efficacy adequate to justify approval; however they also recommended getting careful post-approval data. The observation of benefit primarily in the female subset was not viewed as having implications for labeling. Some members stated a preference for a more clinically relevant outcome than FVC, and some expressed a sentiment for liberalizing p-value criteria in diseases as rare and difficult, but important, to study as this.

The Division determined that the advice received from the Advisory Committee for the Aldurazyme application was generally applicable to the Naglazyme application, and that the Naglazyme application did not raise new issues of a nature that required additional Advisory Committee input.

## Trade Name Review

BioMarin initially proposed the trade name for this product. The Division and DDMAC concurred on rejecting the name on the grounds that the

implying a unique effectiveness that had not been demonstrated. BioMarin's subsequent proposal of "Naglazyme" was considered acceptable by DMETS, DDMAC, and the Division.

## Regulatory conclusions

In the opinion of this reviewer, the data in this application support approval of Naglazyme under 21 CFR 601 for treatment of MPS VI at a dosage regimen of 1 mg intravenously every week, and provide a basis for construction of product labeling that contains the essential scientific information needed for the safe and effective use of Naglazyme.

The product labeling should identify that the benefit was reflected as improvement in walking and stair climbing. It should contain a warning about the risks and management of infusion reactions. It should indicate the lack of information about safety and efficacy for children younger than 5 years.

BioMarin has agreed to appropriate and adequate post-marketing commitments as described above; these include commitments to conduct a long-term registry study to collect additional safety and efficacy data, [redacted] to obtain non-rodent reproductive toxicity studies, to improve the clinical antibody and product assays, and to make various improvements in the manufacturing process.

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | BLA |
| Submission Number | **125117/0** |
| Submission Code | BLA |
| | |
| Letter Date | November, 23, 2004 |
| Stamp Date | November 29, 2004 |
| PDUFA Goal Date | May 31, 2005 |
| | |
| Reviewer Name | Ilan Irony<br>Division of Therapeutic Biological<br>Internal Medicine Products<br>Office of New Drugs – CDER - FDA |
| Review Completion Date | May 26, 2005 |
| | |
| Established Name | Galsulfase |
| (Proposed) Trade Name | Naglazyme |
| Therapeutic Class | Enzyme Replacement Therapy |
| Applicant | BioMarin Pharmaceutical Inc. |
| | |
| Priority Designation | P |
| | |
| Formulation | 1 mg/mL solution, in 5.3 mL vial |
| Dosing Regimen | 1 mg/kg IV weekly |
| Indication | Mucopolysaccharidosis Type VI |
| Intended Population | Mucopolysaccharidosis Type VI |

## Table of Contents

## LIST OF FIGURES

# 1 EXECUTIVE SUMMARY

This document is the Medical Officer's Clinical Review of galsulfase (recombinant human arylsulfatase B), a new molecular entity. The indication sought is "for patients with mucopolysaccharidosis type VI (MPS VI)." MPS VI is a rare genetic disorder that results from a mutated sulfatase enzyme involved in the catabolism of glycosaminoglycans (GAGs), specifically dermatan sulfate. The lysosomal accumulation of GAGs causes impairment and gradual destruction of tissues and organs, and leads to severe morbidity and mortality of the affected patients. The phenotypic presentation of this disorder is quite variable, as is the course of the disease, with severely affected patients dying in the first decade of life, and more mildly affected patients living until their fourth decade.

MPS VI causes a multitude of symptoms and signs, but most of the morbidity and mortality is consequent to effects on joints, and the cardiovascular and respiratory systems.

Galsulfase has been developed by insertion of the recombinant DNA into Chinese Hamster Ovary cells, with steps added to purify and concentrate the enzyme. Before the clinical development of Galsulfase, BioMarin had conducted pharmacodynamic in vitro studies in fibroblasts from MPS VI patients, and in vivo studies in a feline model of MPS VI.

A total of 58 subjects with MPS VI have been exposed to weekly intravenous infusions of galsulfase, with durations ranging from 24 to 144 weeks. Two of these subjects were not participants in BioMarin clinical trials.

## 1.1 Recommendation on Regulatory Action

Due to the multifaceted nature of the disease, assessment of clinical benefit is necessarily complex. FDA and BioMarin prospectively agreed that outcomes that indicate increased endurance in adequate and well controlled studies would be accepted as evidence of efficacy in the treatment of patients with MPS VI. Although endpoints such as mortality or specific cardiovascular or respiratory outcomes would be desirable for demonstration of efficacy in a lethal condition such as MPS VI, use of these endpoints is not feasible in the context of a disease that is both chronic and rare. The distances walked in a standardized 6-minute walk test, or a 12-minute walk test, are thought to integrate motor function with indirect evidence of improvement in articular, cardiovascular and respiratory capacities; all of these are affected, with variable severity, among patients with MPS VI.

In the clinical studies conducted under this license application, BioMarin first investigated the ability of galsulfase to increase the walking distance in the 6-minute walk test in a dose controlled study of 24 weeks in 7 subjects with MPS VI. Most subjects had variable increases in distance walked in the 6-minute test. After completion of 24 weeks into the study, BioMarin decided to treat all subjects with the higher of the 2 doses, 1 mg / kg weekly, in an open label extension to the study. Subjects treated for an additional period of 120 weeks demonstrated additional improvement in distance walked. The improvement observed was highly variable, and

was confounded by complications of the disease. The study was not controlled, and the response in endurance was so variable as to not allow any conclusions on the magnitude of benefit.

A Phase 2 study enrolled 10 subjects for an open label experience with weekly galsulfase infusions at the 1 mg / kg dose for 72 weeks. That study demonstrated improvements in distance walked, with the greatest improvements from baseline noted in the subjects who could walk the least at baseline. Table 1 below shows the data on the distances walked in the 12-minute walk test:

**Table 1 Study ASB-01-04, 12MWT Results in Ascending Order by Baseline 12MWT Distances**

| | Baseline (m) | | Week 48 (m) | | Change at Week 48 (m) | | % Change at Week 48 | |
|---|---|---|---|---|---|---|---|---|
| Subject | 6 Min | 12 Min | 6 Min | 12 Min | 6 Min | 12 Min | 6 Min | 12 Min |
| 200 | 19 | 33 | 83 | 156 | +64 | +123 | +334% | +378% |
| 300 | 101 | 101 | 146 | 280 | +46 | +180 | +45% | +179% |
| 303 | 85 | 101 | 174 | 330 | +89 | +229 | +104% | +227% |
| 203 | 84 | 146 | 140 | 266 | +57 | +120 | +68% | +82% |
| 304 | 172 | 215 | 408 | 810 | +237 | +595 | +138% | +277% |
| 201 | 138 | 254 | 286 | 536 | +148 | +282 | +108% | +111% |
| 202 | 215 | 410 | 330 | 644 | +115 | +234 | +53% | +57% |
| 302 | 221 | 435 | 310 | 618 | +90 | +183 | +41% | +42% |
| 204 | 247 | 472 | 252 | 519 | +6 | +47 | +2% | +10% |
| 301 | 245 | 475 | 308 | 595 | +64 | +120 | +26% | +25% |

This study was uncontrolled and conducted as an open label experiment, and cannot provide persuasive evidence of efficacy. In addition to this phase 2 study, BioMarin conducted an observational survey of 121 subjects with MPS VI to determine the range of clinical features in the disease, including the distances walked in 6 and 12 minutes, and ability to climb stairs.

The Phase 3 study was conducted in subjects with a protocol-specified impairment in their 12-minute distance walked during screening within a 5 – 400 meter range. Unfortunately, the randomization process in this relatively small study of 39 subjects yielded a substantial imbalance between the two groups in distance walked at baseline, directionally in favor of the placebo group (227 ± 170 meters for the galsulfase group and 381 ± 202 meters for the placebo group). The magnitude of imbalance was actually larger than the observed treatment effect in the galsulfase group during the 24 weeks of the controlled study, making interpretation of the results difficult. With the longitudinal analysis model used, the mean between groups difference in the 12 minute walk test was 92 ± 40 meters in the change from baseline to Week 24, with a statistically adjusted baseline common to both treatment groups ($p = 0.025$). Other sensitivity analyses supported the findings of improved distance walked in the 12-minute walk test in galsulfase-treated subjects.

The imbalance noted at baseline with the distances walked raised concerns during the review of this application in two areas: a differential regression to the mean for the galsulfase-treated group, as compared to the placebo-treated subjects, and a ceiling effect for the placebo-treated subjects. This reviewer conducted an analysis to address the concern of regression to the mean for the galsulfase subjects. A comparison of distances walked by 36 subjects in the Survey Study and the distances walked by the same subjects in the Phase 3 study 1 to 2 years later demonstrated that there were no differential worsening in distances walked by the subjects who

would be randomized to galsulfase in the Phase 3 study, as compared to those randomized to placebo.

The other concern was that the placebo-treated subjects would have reached their ceiling distance at baseline, such that no further improvement would be expected from an intervention. The open label extension to the Phase 3 study demonstrated that placebo-treated subjects, while having essentially no improvement (26 ± 122 meters) in the controlled portion of the study, were able to sustain an improvement of 66 ± 133 meters once they were switched to weekly galsulfase for 24 weeks in the extension study. The change was important in demonstrating that further improvement in distance walked could be achieved.

The secondary endpoint in the placebo-controlled study, the rate of stair climbing, was also supportive of the efficacy of galsulfase in increasing endurance of subjects with MPS VI, despite the between-group imbalance in the rate of stair climbing at the baseline of the Phase 3 study.

BioMarin has demonstrated an unequivocal reduction of urinary GAG levels with treatment with galsulfase in all subjects treated in the three studies reported in this application. There has been no demonstration that a reduction of urinary GAGs correlates with clinical benefits in any area of impairment in patients with MPS VI.

The safety of galsulfase infusions in the treatment of these subjects was assessed in the 3 clinical studies of these 56 subjects and the extension to these studies. Serious AE's that were determined to be caused by galsulfase included apnea during infusion in one subject with a history of severe airway compromise, asthma exacerbation hours after galsulfase infusion in another subject, and a severe urticarial reaction in a third patient during infusion, after milder reactions were noted during previous infusions. Most adverse events that were attributed to galsulfase occurred during infusions. The more common of these events were fever, rigors, headache, nausea and vomiting, and rash and urticaria. Most of these adverse events were ameliorated by slowing the rate of intravenous infusion, by adding more anti-histamines or by adding glucocorticoid steroid treatment or prophylaxis prior to infusions.

All but one subject treated with galsulfase developed anti-galsulfase IgG antibodies over a period of 4 – 12 weeks, with the titers decreasing over one year of treatment. Presence of anti-galsulfase antibodies and their titers inversely correlate with the concentration of native enzyme. The studies have shown no evidence that these antibodies are associated with adverse events, higher rate or increased severity of infusion reactions, anaphylaxis or complement activation.

While the risks of infusion cannot be ignored, and must be taken seriously as part of the overall treatment of patients with MPS VI, they are small compared to the potential benefit of galsulfase in a condition where no effective alternative therapies are available and where there are fatal outcomes at an early age. The risk / benefit profile derived from the evidence extracted from this application is favorable, supporting approval of galsulfase in the treatment of MPS VI patients.

It is important to emphasize that this approval of galsulfase is a standard approval, based on demonstration of clinical benefit in increasing endurance, and not as accelerated approval.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

BioMarin's risk management plan consists of two distinct programs:

- Pharmacovigilance / Safety Reporting Program: this program will follow appropriate regulations and guidelines for monitoring, collecting and reporting adverse events in patients receiving galsulfase treatment in the postmarketing setting.
- Clinical Surveillance Program: this program is design to collect and analyze data regarding both the natural history of MPS VI, as well as the safety and efficacy of galsulfase treatment in a voluntary, registry-like, commercial setting. This will be an ongoing observational database to track specific clinical outcomes of patients with MPS VI, including but not limiting to those receiving long-term treatment with galsulfase.

### 1.2.2 Required Phase 4 Commitments

- The Clinical Surveillance Program described above will be a Registry of patients with MPS VI to track long term safety and risk management, as well as long term clinical efficacy of galsulfase. This Registry will need to monitor also the long term safety and efficacy of galsulfase in pregnancy and lactation, as well as in children with MPS VI younger than 5 years of age.
- Dose exploration during the development of galsulfase has been limited, and there is no evidence that the proposed dose and / or regimen will provide optimal risks / benefits. BioMarin has committed to conducting a randomized dose-ranging study in infants with MPS VI to evaluate effects on growth and development.

### 1.2.3 Other Phase 4 Requests

- Improvement of the assays to detect anti-galsulfase antibodies(IgG and IgE), to be used in the registry patients and the post-marketing commitment studies, will be beneficial.
- BioMarin needs to improve the assays intended to measure ASB mass concentration and activity.
- Study of intra-articular galsulfase administration in the most severely affected joints, given that galsulfase has been shown to provide increased pharmacodynamic activity when injected in affected joints in the feline model, and the BioMarin's data, though limited, suggest that galsulfase penetrates the articular space poorly with systemic administration.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Three main studies were conducted in this population to support approval of galsulfase. A Phase 1 / 2 study involving 7 subjects who were randomized to either 0.2 mg / kg or 1 mg / kg of weekly galsulfase for 24 weeks, followed by an extension study in which all remaining subjects were converted to the 1 mg / kg dose and followed for a total of 144 weeks; a Phase 2 study of 10 subjects treated with galsulfase at 1 mg / kg dose for 72 weeks, and a Phase 3 randomized, placebo-controlled, multinational study of 39 subjects followed for 24 weeks, leading in to an open label uncontrolled extension study, still ongoing, in which all subjects have been treated with galsulfase 1 mg / kg weekly. The overall safety database is 56 subjects, with subjects exposed to galsulfase treatment for periods ranging from 24 weeks (19 subjects) to 144 weeks (5 subjects).

### 1.3.2 Efficacy

In this very rare patient population of MPS VI, FDA has accepted the concept that a single clinical trial, providing robust evidence of benefit, could serve as an adequate basis for approval, providing that the safety data lead to a favorable risk-benefit assessment. Efficacy endpoint data from a single placebo-controlled study were compared to data findings from the same or similar endpoints in previous smaller, uncontrolled studies to add strength to the evidence in support of galsulfase efficacy in patients with MPS VI.

The primary efficacy endpoint in the pivotal study 03-05 was the distance walked in a 12-minute walk test, analyzed in both galsulfase- and placebo-treated subjects from baseline through 24 weeks of the study in a repeated measures longitudinal model, as a change from baseline.

Secondary efficacy endpoints in Study 03-05 were:

- the rate of climbing stairs in a 3-minute stair climbing test, also analyzed as a comparison between groups through a repeated measures longitudinal model, as a change from baseline. This endpoint is also a measure of endurance for subjects with MPS VI.
- urinary GAGs levels, both as a change from baseline to week 24 in the different groups, as well as the proportion of responders (defined by BioMarin as subjects whose urinary GAGs levels at Week 24 were reduced at least 50 % from baseline).

The Phase 3 study, Study 03-05, was a multicenter, multinational, randomized, placebo-controlled study aimed at demonstrating the efficacy and safety of galsulfase through 24 weeks. This study was followed by an open label extension study, study 03-06, in which all subjects who completed the Phase 3 controlled study would be eligible to participate and would receive treatment with galsulfase. BioMarin agreed to submit the initial 24 weeks of endurance data (12 minute walk test distances and rates of stair climbing) in study 03-06 to support the efficacy findings of the controlled study. Study 03-06 is ongoing at the time of this review.

Inspections at foreign sites have provided no evidence to suggest major problems with study conduct that would preclude interpretation of the data. The blinding and randomization process appeared to be intact. The statistical analysis plan was implemented in accordance with FDA's prior agreements, without evidence of bias.

The main problem in the interpretation of efficacy data with respect to both endurance-related endpoints was the presence of substantial baseline imbalance. Table 2 can quickly illustrate the magnitude of this problem:

**Table 2. Distances walked in the 12 MWT over time in Study 03-05**

| Timepoint | Galsulfase | | Placebo | | Between-Group Difference (Mean ± SE) |
|---|---|---|---|---|---|
| | n | Mean ± SD (meters) | n | Mean ± SD (meters) | |
| Baseline | 19 | 227 ± 170 | 20 | 381 ± 202 | -154 ± 60 |
| Week 24 | 19 | 336 ± 227 | 19 | 399 ± 217 | - 63 ± 72 |
| Week 24 - baseline | 19 | 109 ± 154 | 19 | 26 ± 122 | 83 ± 45 |

The mean difference between groups in distance walked in the 12 minute walk test at baseline was 154 meters, favoring the placebo group. This is a substantial imbalance, considering that the mean difference in improvement in 12-minute walk tests from baseline to Week 24 was only 83 meters in favor of galsulfase. When statistically adjusted for baseline to fit the longitudinal model, the difference between groups in the 12-minute distance walked was 92 ± 40 meters ($p = 0.025$, 95 % CI: 11 – 172 meters). The specific concerns FDA had with interpretation of these data were the potential for regression to the mean that would be affecting galsulfase-treated subjects more than placebo-treated subjects and the potential for a ceiling effect for placebo subjects, with no further improvement to be expected.

In order to address the potential for regression to the mean, FDA assessed the distances walked by 36 of the 39 Phase 3 subjects during the survey study conducted 1 to 2 years prior to the enrollment in study 03-05. The slopes of changes in distances walked between the time of the survey and the time of baseline in study 03-05 were no different between the subjects who were ultimately randomized to galsulfase versus those who were randomized to placebo. FDA also compared the distances walked at screening to the distances walked at baseline (the time difference from screening to baseline being days to several weeks) in Study 03-05. Again there was no evidence of worsening in galsulfase-treated subjects, for which regression to the mean would be expected.

To address the concern of a ceiling effect in the placebo-treated subjects, FDA compared the distances walked by the placebo subjects for 24 weeks in study 03-06, after being switched to active treatment with galsulfase. These subjects entered study 03-06 without being aware of their treatment allocation in the double blind phase, study 03-05. This blinding contributed to minimize any potential expectation bias that the knowledge of treatment change (placebo to

galsulfase) might have contributed to the walking distance. The combined results of the distances walked in the 12 MWT in the 24 weeks of the controlled study 03-05 and the first 24 weeks of study 03-06 are shown in Table 3:

**Table 3. Combined results of 12 MWT distances in Study 03-05 (baseline and week 24) and the first 24 weeks of Study 03-06**

| Timepoint | Galsulfase | | Placebo → Galsulfase | |
|---|---|---|---|---|
| | n | Mean ± SD (meters) | n | Mean ± SD (meters) |
| Baseline | 19 | 227 ± 170 | 20 | 381 ± 202 |
| Week 24 | 19 | 336 ± 227 | 19 | 399 ± 217 |
| Week 48 | 18 | 372 ± 240 | 18 | 482 ± 206 |

Whereas subjects originally treated with galsulfase experienced a small increase in walking distance during study 03-06 (Weeks 24 to 48), the subjects originally treated with placebo who were switched to galsulfase experienced a substantial improvement in walking distance during the first 24 weeks of the extension study. These data decrease the concern of a potential ceiling effect exhibited by the placebo subjects at baseline. In addition to 12 MWT data from this study, the mean distances in the 12 MWT and the 6 minute walk test (6 MWT) have been shown to improve in the other studies conducted during galsulfase clinical development. These studies were smaller, one dose controlled, and the other uncontrolled, but they are supportive of the findings in the Phase 3 study.

Very similar between-groups imbalances at baseline were noted for the secondary endpoint of rate of stair climbing (Table 4).

**Table 4. Rate of stair climbing in Studies 03-05 and the first 24 weeks of Study 03-06**

| Timepoint | Galsulfase | | Placebo → Galsulfase | |
|---|---|---|---|---|
| | n | Mean ± SD (stairs/min) | n | Mean ± SD (stairs/min) |
| Baseline | 19 | 19 ± 13 | 20 | 31 ± 18 |
| Week 24 | 19 | 27 ± 17 | 19 | 33 ± 20 |
| Week 48 | 18 | 30 ± 16 | 18 | 40 ± 19 |

The between-groups difference in improvement (Week 24 minus baseline) was 6 ± 3 stairs/ minute in favor of galsulfase. Once placebo subjects were switched to galsulfase, there tended to be benefit in this group as well (Week 48 minus Week 24), decreasing somewhat the concern regarding a ceiling effect in the placebo group.

At Week 24, the excretion of urinary GAGs had decreased by 73 % in the galsulfase-treated group, with almost no change in the placebo group ($p < 0.001$). The drop was rapid, most of it

being observed by week 4, persistent over time (up to 144 weeks in the Phase 1 study), and consistent across treated subjects. Seventeen of the 19 galsulfase-treated subjects had urinary GAGs reduced to < 50 % of baseline, whereas none of the placebo subjects had such responses.

The data for the tertiary endpoints, such as joint range of motion, quality of life measures, etc. were not as clear in pointing to a galsulfase benefit.

The overall development of galsulfase for assessment of efficacy involved relatively few subjects, and the pivotal Phase 3 study was conducted in only 24 weeks, in a condition that is progressive and life-long. The limitation in sample size is a function of the very low prevalence of the condition; the relatively brief study duration is related to the lack of alternative modes of effective treatment for a condition that has a variable course but fatal outcome (i.e., the difficulty of maintaining subjects on placebo for an extended period under these circumstances). The design of the studies in this development was coherent and clear, although longer studies might have been able to show a treatment effect in more compelling and clinically important outcomes, i.e., cardiovascular and respiratory function. Other study limitation are

- lack of efficacy data on children younger than 5 year of age, a population that at least in theory is more likely to reap benefits, before organ dysfunction is significant and widespread.
- lack of a full exploration of dose and regimen of administration, attributable to the rarity of the disease / scarcity of subjects and the need to establish a dose reasonably expected to exert both pharmacodynamic and clinical effects.

This reviewer's conclusion is that BioMarin was able to demonstrate, through a rigorous development, substantial evidence of efficacy of galsulfase in the treatment of patients with MPS VI. Currently there are no effective and safe treatments available for MPS VI, short of palliative and supportive care, and in a few desperate cases, bone marrow transplantation. The latter is effective to correct some of the clinical abnormalities associated with MPS VI, but at a cost of substantial morbidity and mortality.

### 1.3.3 Safety

The entire safety database consists of 56 subjects, studied for periods of 24 to 144 weeks. The dose of galsulfase used in 53 of these subjects was 1 mg / kg weekly. Four subjects in study 00-01 had received a galsulfase dose of 0.2 mg / kg weekly for periods of 3 to 30 weeks, and two of these continued to receive galsulfase at 1 mg / kg for over 110 weeks.

There was one death in this product's development, that was unrelated to galsulfase: a subject in study 00-01 who withdrew from the trial at Week 3 developed a malignant brain glioma and colorectal carcinoma, and died 20 months after the last dose infused. Notable SAE's temporally related to galsulfase infusion included severe allergic / urticarial reaction, an episode of apnea, and asthma exacerbation occurring hours after infusion.

Most infusion reactions were mild to moderate, and included fever, rigors, headache, nausea and vomiting, and rash and urticaria. These infusion-related adverse events were more common with galsulfase treatment than with placebo. Most reactions decreased in frequency and intensity by

slowing the infusion rate or by adding additional anti-histamines, and a few needed treatment or prophylaxis with glucocorticosteroids for periods of several weeks at a time.

The 3 studies together reported 1511 adverse events: 1167 among galsulfase-treated subjects (n=36) and 344 among placebo-treated subjects (n = 20). The most common non-infusion events were headaches, nausea and vomiting, and upper respiratory infections.

All but one galsulfase-treated subject developed anti-galsulfase IgG antibodies after exposures beyond 4 weeks. The titers of these antibodies generally rose and reached a peak at week 48 then declined substantially sometimes to titers below the limit of detection. The presence of anti-galsulfase antibodies does not appear to neutralize the enzymatic activity (as seen by continuous suppression of urinary GAG). The peak of antibody titers does not appear to be associated with increased frequency or severity of adverse events, infusion associated reactions, complement consumption or other laboratory abnormalities.

The very small number of subjects exposed to the lower dose of galsulfase (4 subjects) does not allow a meaningful comparison of incidence of adverse events across different doses. The majority of the safety experience with galsulfase comes with the 1 mg / kg dose, the dose proposed in this license application.

The main limitations in the evaluation of galsulfase safety come from the very small sample of subjects studied and the background of multiple morbid events to be expected in MPS VI.

Galsulfase shows a reasonable safety profile, primarily associated with infusion reactions, in a condition that carries high morbidity and mortality, and for which no safe and effective therapies exist. Infusion reactions are managed with slowing the rate of infusion and pre-treatment with anti-histamines; both of these recommendations are present in BioMarin's proposed labeling.

### 1.3.4 Dosing Regimen and Administration

The dose of galsulfase proposed is 1 mg / kg of body weight, given intravenously on a weekly basis. The infusions should be preceded by oral administration of anti-histamines, and should be conducted over a 4 hour period, and could be extended to periods of up to 20 hours, if needed to attenuate infusion-associated reactions. Pre-treatment with steroids should only be considered for severe infusion reactions and for short periods (weeks to several months) of duration.

### 1.3.5 Drug-Drug Interactions

No formal drug interactions studies were conducted in the development of galsulfase. Galsulfase has consistently been infused after administration of anti-histamines in the clinical trials reported in this submission. All safety information is related to the concomitant use of anti-histamines.

### 1.3.6 Special Populations

We have not identified special populations regarding the product's use.

# 2 INTRODUCTION AND BACKGROUND

This document is the medical officer's review of the clinical data submitted with the Biologics License Application Submission Tracking Number 125117/0. This application is for Galsulfase (Naglazyme), a recombinant enzyme product which is proposed for use as enzyme replacement therapy for patients with Mucopolysaccharidosis Type VI.

Lysosomal storage disorders result from a genetic defect that causes deficient production or function of one or more of the lysosomal enzymes. The enzymatic deficiency results in an abnormal accumulation of metabolites within a lysosome and ultimately disruption of the normal cell function and cell death. Lysosomal storage disorders are usually classified according to the nature of the macromolecule that is abnormally catabolized and consequently accumulates within the lysosome. Sphyngolipidoses (including gangliosidoses) are associated with the accumulation of complex lipids, the basic structure of which is a sphingosine, a long chain amino-alcohol. Oligosaccharidoses or mucolipidoses are associated with the storage of complex glycoproteins. Mucopolysaccharidosis are caused by deficiencies of enzymes needed to degrade glycosaminoglycans (also known as mucopolysaccharides). Glycosaminoglycans themselves are lysosomal degradation products derived by proteolytic removal of the protein core of proteoglycans (macromolecules occurring in the cell membrane and extracellular matrix). Mucopolysaccharidosis VI is the subject of this license application, and will be described here briefly.

Mucopolysaccharidosis Type VI (MPS VI) is characterized biochemically by the deficiency of the lysosomal enzyme arylsulfatase B (ASB), also known as N-acetylgalactosamine 4-sulfatase. The condition is also known as Maroteaux-Lamy Syndrome.

The enzyme hydrolyzes the sulfate moiety of dermatan sulfate, a glycosaminoglycan. 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 progressive disorder with multiple organ and tissue involvement. As with other mucopolysaccharidosis, there is a continuum of severity in the clinical presentation of these patients. The mildest form of the disease is characterized by short stature, corneal clouding, Legg-Perthes-like disease of the hips, and aortic stenosis. The classic form has severe physical changes, most importantly progressive deceleration of growth, skeletal deformities, coarse facial features, hydrocephalus due to meningeal involvement, upper airway obstruction, heart disease and joint deformities. The diagnosis of MPS VI is usually made at 6-24 months of age. Death usually results from respiratory infection or cardiac disease when patients reach their second decade of life, although patients with milder manifestations may survive until their fourth decade. MPS VI is not typically associated with progressive impairment of mental status, although physical limitations may impact learning and development. In all forms of the disease striking azurophilic cytoplasmic leukocyte inclusions (Alder granules) and deficiency of arylsulfatase B (N-acetylgalactosamine 4-sulfatase) are found.

The gene coding for this enzyme is located in chromosome 5, at the locus 5q11-q13. Of the 45 clinically relevant enzyme genetic mutations, the majority are missense mutations (31 of the 45).

A level of enzyme of at least 5% of the normal enzyme activity and enzyme concentration seems to be necessary to avoid clinical symptoms.
ASB can be found in high intracellular concentrations in eosinophils, and there is evidence that ASB inactivates slow reacting substance of anaphylaxis (SRS-A) and modulates allergic inflammatory reactions.

## 2.1 Product Information

Galsulfase is the recombinant form of human N-acetylgalactosamine-4-sulfatase, also known as arylsulfatase B. The proposed trade name is NAGLAZYME.

This product is a new molecular entity, a biologic in the class of human proteins made through recombinant DNA technology.

This recombinant enzyme aims to correct at least partially the deficiency of native arylsulfatase B in patients with MPS VI.

The proposed indication is the treatment of patients with MPS VI, specifically to improve physical endurance, with evidence based on increased walking and stair climbing capacity. There are no limitations on age groups or other demographic parameters, although the clinical studies were conducted in patients older than 5 years of age. The proposed dose is 1 mg / kg of body weight, administered intravenously once weekly.

## 2.2 Currently Available Treatment for Indications

No currently approved treatment is available for patients with MPS VI. Current treatment of affected individuals is restricted to symptomatic and palliative therapies and procedures. Bone marrow transplantation has been used in patients with MPS VI, with demonstrated long-term benefits in a few patients, but the procedure carries substantial morbidity and mortality, and is currently reserved for rapidly progressive forms of the disorder in young children. Supportive care is usually provided for specific complications of MPS VI.

## 2.3 Availability of Proposed Active Ingredient in the United States

The product is not currently marketed in the United States of America or anywhere in the world.

## 2.4 Important Issues With Pharmacologically Related Products

The only product that is pharmacologically related to galsulfase is Aldurazyme (laronidase), an approved biologic product, licensed for the treatment of patients with MPS I, also known as Hurler's or Hurler-Scheie syndrome. The conditions are similar in their clinical presentation, and the galsulfase development approach used by BioMarin is similar to that of laronidase, also manufactured by BioMarin. Important safety issues that became apparent in studies with Aldurazyme were related to infusion reactions, that could be as serious as anaphylaxis. The important post-marketing commitments at the time of Aldurazyme licensing were:

- the improvement in the IgE and neutralizing antibody assays used in the monitoring of antibody responses in post-marketing studies;
- further exploration of the effect of different doses and dosing schedules on the clinical response;
- evaluation of the long term safety and activity of laronidase as tracked through a voluntary patient registry, including gathering of data on pregnancy and lactation;
- evaluation of the treatment effect in subjects younger than 6 years of age.

These became post-marketing commitments that are being implemented at the present time or that have recently been completed.

## 2.5 Presubmission Regulatory Activity

Development of galsulfase occurred under the biologics IND 9057. The original IND application was submitted to the FDA on April 28, 2000. BioMarin and FDA discussed plans for a Phase 3 study on June 24, 2003 (End-of-Phase-2 meeting). A Pre-BLA meeting was held between BioMarin and FDA on September 28, 2004.
Galsulfase received orphan drug designation # 98-1198 on February 12, 1999, and Fast Track designation on June 26, 2000.

## 2.6 Other Relevant Background Information

Galsulfase is not approved in other countries and there is no foreign labeling available for review.

# 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

## 3.1 CMC (and Product Microbiology, if Applicable)

### 3.1.1 Formulation change

After the completion of the dose-controlled portion of the Phase 1 / 2 study 00-01, at Week 84, BioMarin added polysorbate 80 as a — . to the drug product formulation. A pharmacokinetic crossover study showed comparability between the formulations with and without polysorbate 80.

### 3.1.2 Other changes

Along with the addition of polysorbate 80 to the formulation of the drug product, the production process was moved from the — BioMarin BMK facility — process to a — process, — The Phase 2 and Phase 3 clinical studies were conducted with product manufactured under this process. The manufacturing of galsulfase was subsequently moved from the BMK facility to the Galli Drive facility. The change was designated by BioMarin as a change from the clinical product to a commercial product. The — — . No clinical studies were conducted with the product obtained under the commercial scale production process. Characterization of the comparability from the chemistry standpoint, as well as from the clinical pharmacology standpoint are currently under review.

## 3.2 Animal Pharmacology/Toxicology

The non-clinical pharmacology, toxicology and pharmacokinetics of galsulfase were evaluated using in vitro and in vivo animal studies. The in vitro studies were conducted in fibroblasts obtained from normal volunteers as well as from patients with MPS VI, and has shown cellular uptake and lysosomal internalization, as well as evidence of sulfatase activity.

Murine and feline models of MPS VI have been developed and characterized. The pre-clinical development of galsulfase made extensive use of studies in cats with MPS VI, regarding pharmacodynamic effects. These animals manifest facial dysmorphia (small head and ears, broad maxilla), diffuse corneal clouding, bone abnormalities (epiphyseal dysplasia, subluxations, pectus excavatum), reduced body weight, reduced cervical spine flexibility, posterior paresis related to thoraco-lumbar spinal cord compression, osteoporosis, degenerative joint disease, mild hepatosplenomegaly, thickened heart valves, and absence of CNS lesions. Laboratory findings include peripheral leukocyte, hepatocyte and Kupfer cell granulation, increased excretion of GAGs and dermatan sulfate. Most of these studies were conducted under the supervision of — — These studies provided BioMarin the opportunity to evaluate the

effects of intravenous infusions, and exploration of dose levels and infusion schedules. In order to unmask any effects of immunogenicity of a heterologous protein, some studies were undertaken in cats with MPS VI using the recombinant feline ASB.

Toxicology testing was conducted in rats and dogs, through acute toxicity studies in which galsulfase was administered as a bolus intravenous injection to rats and as a four hour infusion in dogs. Chronic administration of galsulfase to evaluate toxicity was conducted in a 27-week repeated dose study in Cynomolgus monkeys. Reproductive toxicology was investigated in rats to examine effects on fertility and early embryonic development. Genotoxicity studies were not conducted, but these are generally thought to be unnecessary, as the product is a recombinant human glycoprotein with low mutagenic potential.

Non-clinical pharmacology (pharmacokinetics and biodistribution) studies were done in MPS VI cats. Toxicokinetic assessments were performed in single-dose toxicity studies in dogs, as well as in the 27-week repeated dose toxicity study in Cynomolgus monkeys. Pharmacokinetic studies in animals were performed to investigate comparability of galsulfase after changes in manufacturing were implemented.

The important findings from the non-clinical program are:

- Younger MPS VI cats appear to derive more benefit than older cats.
- Galsulfase administered as a 2-hour infusion is associated with improved tissue distribution compared to bolus intravenous administration, and decreased infusion-associated reactions.
- The tissue ½ life of galsulfase in normal cats following infusion of 1 mg / kg of galsulfase is 2.4 to 4.2 days, which BioMarin used as a basis for the once weekly schedule of administration.
- Monthly intra-articular injections of galsulfase in severely affected joints in cats with MPS VI combined with weekly intravenous administration provided more improvement in joint pathology as compared to intravenous weekly infusions alone.
- Study ASB-PC-00-02 was conducted in newborn felines affected by feline MPS VI. In that study, newborn cats received weekly doses of recombinant human galsulfase at 0.2, 1 or 5 mg/kg over a 5- to 11-month period. The 5 mg /kg dose was clearly better in not only reducing GAGs from liver Kupfer cells (the only benefit demonstrable at the 0.2 mg / kg dose level), but also by providing greater flexibility, less spinal cord compression, increased bone mineral density, as well as GAG clearance from heart valve, aorta, skin, dura, liver cells and brain perivascular cells. A study conducted in —— laboratory, compared the 5 mg / kg dose of recombinant human enzyme administered to 3 cats to the 1 mg / kg of the recombinant feline enzyme administered to 2 cats over a period of up to 170 days, and conclude that the magnitude of pharmacodynamic effect of the 1 mg / kg of feline enzyme was equivalent to that of the 5 mg / kg of human enzyme in the BioMarin study. BioMarin concluded that if using homologous (same species) galsulfase, the magnitude of the pharmacodynamic effect is greatest with 1 mg / kg.
- One cat with MPS VI who developed anti-galsulfase antibodies during treatment with galsulfase experienced a temporary reversal of the apparent clinical improvements observed with initial treatment. This cat had neutralizing antibodies as determined by an in vitro assay.

The same animal subsequently continue to experience clinical improvement while the antibody levels fluctuated.

- In the early studies that were using rhASB from Dr — laboratory, there were infusion associated reactions that ranged from mild hypersensitivity to repeated anaphylactoid, anti-histamine resistance reactions. With the BioMarin galsulfase product used in later animal studies (with polysorbate 80 added to the formulation), these reactions subsided.
- The acute toxicity studies primarily demonstrated swelling of the face and paws of animals receiving bolus intravenous doses as high as 10 to 20 mg / kg. The event was judged to be related to the dose of polysorbate 80 injected. In Cynomolgus monkeys treated in the 27-week study, doses of 3 and 10 mg / kg were associated with minimal bile duct hyperplasia and periportal inflammation.
- Study reports documenting chronic active lung inflammation and lymphocytic infiltrates in liver, spleen and kidney in Cynomolgus monkeys are currently being reviewed by FDA's pharmacology / toxicology reviewer. In addition, pathology findings in cats with MPS VI treated with galsulfase suggestive of glomerulonephritis and possibly immune complex depositions are being reviewed at the time of this clinical review. The clinical studies did not suggest toxicity of this nature, although lung and upper airway disease are very prevalent in this patient population, and it is unlikely that uncommon toxicities could be detected in the limited sample of MPS VI patients studied in the clinical program. Although there is evidence of complement consumption in one subject in a clinical study after infusion, there is no evidence of any clinical consequence related to this laboratory finding.

# 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

## 4.1 Sources of Clinical Data

Clinical Data available for this review originated from the clinical studies and the survey study conducted by BioMarin, as well as review of the literature references on MPS VI, and the Online Mendelian Inheritance in Man database from the Johns Hopkins University and the National Library of Medicine.

No data were derived from external consultants or advisory committee meetings.

## 4.2 Tables of Clinical Studies

Table 5 contains an overview of the clinical studies reviewed under this application. They were conducted with the purpose of investigating of the safety and efficacy of galsulfase in the treatment of patients with MPS VI. This reviewer has made extensive use of data from a survey study conducted by BioMarin (Study 00-02), not included in the Table 5.

Study 03-05 was the only controlled study in the development program, and provided the primary efficacy data. Study 03-06 was an open-label extension of 03-05, in which all subjects received the active product. Thus, subjects who had been in the placebo group of study 03-05 and who were switched to galsulfase could provide supportive evidence of efficacy. All subjects in Study 03-06 provided uncontrolled safety data.

In addition, 3 pharmacokinetic studies were conducted during clinical studies 00-01, 01-04 and 03-05. These were reviewed, as well study AXB-XO-001, which is a pharmacokinetic comparability study between the galsulfase produced through the clinical process and the galsulfase produced through the commercial process. Limited data from a treatment study of 2 patients sponsored by an Australian investigator were reviewed and are not included in the Table.

**Table 5. Overview of the Galsulfase Clinical Development Program**

| Study | Design | Study centers / subjects | Completion status / study dates | Treatment Doses | Duration of treatment | Number of subjects |
|---|---|---|---|---|---|---|
| 03-05 | Phase 3 Double-blind, randomized, placebo-controlled | USA: 6<br>Germany: 8<br>England: 6<br>Brazil: 8<br>France: 5<br>Portugal: 6 | Completed<br>7/21/03 to 4/8/04 | 1.0 mg/kg galsulfase once weekly vs. placebo | 24 weeks | galsulfase: 19<br>placebo: 20 |
| 03-06 | Phase 3 Open label, uncontrolled, extension to 03-05 | same as above | Ongoing | 1.0 mg /kg galsulfase once weekly | ongoing | galsulfase: 38 |
| 01-04 | Phase 2 Open label, uncontrolled | USA: 5<br>Australia: 5 | Ongoing (Report dates: 3/29/02 to 12/20/03) | 1.0 mg / kg galsulfase once weekly | Ongoing | galsulfase: 10 |
| 00-01 | Phase 1 / 2, double blind, randomized, dose comparison with open label extension | USA: 6<br>Austria: 1 | Double blind study complete. Extension study ongoing.<br>(Report dates: 9/26/00 to 10/16/03) | 0.2 mg / kg vs. 1.0 mg/kg galsulfase once weekly<br>Extension: 1.0 mg/kg | Ongoing | 0.2 mg/kg: 4<br>1.0 mg/kg: 3 |

## 4.3 Review Strategy

The clinical review was almost entirely based on the clinical data from study reports provided by BioMarin in the license application and from the data presented under the IND for galsulfase (IND 9057). The Integrated Review of Efficacy contains a very detailed review and analysis of the data from a single study, Study 03-05 and its extension study, Study 03-06. Study 03-05 is the only Phase 3 study, and the only placebo-controlled study reported in the application. Where applicable, the Integrated Review of Efficacy also compared the data on efficacy endpoints from this study to the data on efficacy endpoints from other clinical studies. Study 01-04, a Phase 2, open label study of the safety and bioactivity endpoints of galsulfase in 10 subjects with MPS VI, was reviewed by Dr. Anne Pariser (Division of Therapeutic Biological Internal Medicine Products), and is incorporated in this document.

The Integrated Review of Safety takes all exposure to humans under all BioMarin studies into a single review.

Clinical Pharmacology data were reviewed by Dr. Anil Rajpal (Division of Therapeutic Biological Internal Medicine Products) and the statistical data analyses were conducted in close collaboration between this reviewer and Dr. Janice Derr, from the Office of Pharmacoepidemiology and Statistical Science, Office of Biostatistics.

## 4.4 Data Quality and Integrity

Three of the 6 clinical sites were inspected during this review cycle of the galsulfase application. Table 6 shows the sites selected and number of subjects enrolled in each of them:

**Table 6. Phase 3 Study Sites selected for FDA inspection**

| Protocol # | Clinical Site | Number of Subjects |
|---|---|---|
| ASB-03-05 | Site 18 – Paul Harmatz, M.D.<br>Children's Hospital & Research Center<br>747 54th Street<br>Oakland, CA 94609 | 6 |
| ASB-03-05 | Site 20 – Michael Beck, M.D.<br>Johannes-Guttenberg Universitaet<br>University of Mainz<br>Langenbeckstrasse 1<br>55101 Mainz, Germany | 8 |
| ASB-03-05 | Site 21 – James E. Wraith, M.D.<br>Royal Manchester Children's Hospital<br>Pendlebury, Manchester M27 4HA, England | 6 |

The English and German sites were selected for inspection because they exhibited the most robust treatment effect. With exclusion of the data from either of these sites, the study would not have succeeded statistically on the primary endpoint. Using the sponsor's responder analysis, these sites had the highest percentages of responders among the 6 sites. Responder was defined by BioMarin as a subject with more than 80 meters improvement in walking distance from baseline to Week 24 in the 12 MWT in Study 03-05.

Three discrepancies relating to reporting adverse events for the same subject (18-005) were noted from the Oakland site. These were present in the medical chart and were absent in the Case Report Forms. These AE's were minor and did not affect the conclusions of the overall safety and efficacy of galsulfase in this review.

The Mainz, Germany site was found to have several protocol violations: lack of use of an analog scale to rate physical energy level, missing assessments of joint pain and stiffness at some timepoints, lack of vital signs monitoring during a few of the infusions in each of the subjects whose records were reviewed, and missing elements of the informed consent.

The Manchester, England site was also found to have several protocol violations: lack of use of an analogue scale to rate physical energy level, joint pain and stiffness at all timepoints, and some elements of the informed consent form were missing. In addition, complement testing was done on site for subject 002 at Week 1 post-baseline and for all subjects during Week 6, without notification from the sponsor; this could result in some unblinding, but we found no evidence of biased outcomes in these subjects.

## 4.5 Compliance with Good Clinical Practices

All the clinical studies were conducted in compliance with good clinical practices. Subjects have had the opportunity to be informed of the studies goals and risks, and signed informed consents, and investigators conducted the clinical studies with ethical principles. Protocol violations occurred in all studies, but these did not affect the conduct of the studies or their conclusions.

## 4.6 Financial Disclosures

BioMarin provided Form 5434, Financial Interests and Arrangements of Clinical Investigators for all principal investigators and subinvestigators, and all Allergy Reaction Review Board members except for Dr. Dr. was the principal investigator at J. From Dr. received $ 107, 060 from BioMarin for protocol preparation, papers written and presented at conferences, and consulting for protocols and the survey. We cannot conclude that these financial arrangements affect the integrity of the data from that site.

# 5 CLINICAL PHARMACOLOGY

## 5.1 Pharmacokinetics

Pharmacokinetic studies were conducted at pre-specified timepoints during the 3 clinical studies in the galsulfase program.

The clinically important findings from these analyses are described below, for each clinical study:

### 5.1.1 Study 00-01

Plasma ASB was collected for pharmacokinetics assessments at Weeks 1, 2, 12, and 24 for both cohorts and Weeks 83, 84, and 96 for subjects in the 1 mg/kg/week cohort and those from the 0.2 mg/kg/week cohort switched to the higher dose. At least in one subject receiving the lower dose of 0.2 mg / kg galsulfase, the plasma ASB could not be measured because it fell below the limit of detection, at a time that his anti-galsulfase titers were elevated, raising the possibility that anti-galsulfase antibodies can interfere with the ELISA assay for galsulfase serum concentrations.

Comparison of the mean values for $AUC_{0-t}$ (Area under the plasma concentration-time curve from 0 to the final sample with a concentration equal to or greater than the limit of quantitation) or $AUC_{\infty}$ (Area under the plasma concentration-time curve from 0 to infinity) between the 0.2 and 1.0 mg/kg/week cohorts shows an increase far in excess of the 5–fold increase in dose, indicating that the pharmacokinetics of ASB are not linear over this dose range.

Beginning with Week 84, subjects received galsulfase made by a modified manufacturing process — and incorporated — Polysorbate 80 into the formulation. Although the mean values for $AUC_{\infty}$ appear to increase and those for CL to decrease by approximately 25%, there is substantial overlap of the individual values and the small number of patients preclude a conclusion that the pharmacokinetics of the two process products differ. In addition, the pharmacokinetic parameters for Week 96 are in good agreement with those from Week 84 providing further support for the consistency of rhASB pharmacokinetics over time. On the other hand, it is possible that galsulfase produced under the modified process and with Polysorbate added increased the exposure to the product and, at least theoretically, its bioactivity. Since the product derived from the — process was not used in the Phase 3 study, the issue of establishing bioequivalence is not critical.

### 5.1.2 Study 01-04

The mean values (for $AUC_{0-t}$ and $AUC_{\infty}$ in the 10 subjects appeared to increase from Week 1 to Week 2, remain unchanged at Week 12, and then increase slightly at Week 24 . The effect of week was statistically significant for both parameters with Week 1 being statistically different from Weeks 2, 12, and 24; there were no significant differences among the latter three weeks.

The results of this study suggest that beginning with the second dose (Week 2), galsulfase pharmacokinetics appear to be independent of the duration of treatment through at least 24 weeks.

### 5.1.3 Study 03-05

Serial plasma concentrations for the determination of rhASB pharmacokinetics were collected from 14 of the 19 galsulfase-treated subjects at Weeks 1, 2, 12, and 24. The mean values for $AUC_{0-t}$ and $AUC_{\infty}$ were ~2-fold higher on Week 24 than on Week 1. Clearance was significantly lower at Week 24 compared to Week 1. Although the difference was not statistically significant, BioMarin observed that one subject with the highest anti-galsulfase antibody titer (64.9 OD / µL), had a substantial drop in both AUC and clearance. If he is excluded form the analysis (as an outlier), the differences in AUC between Week 1 and Week 24 are significant.

With the exception of the three subjects with antibody levels greater than 10 OD/µL (024-003, 024-005, 026-002), neither clearance nor volume of distribution appeared to be related to antibody level (range of values: — , OD/µL). In those three subjects, both clearance and volume of distribution increased as antibody level increased. However, it is not possible to determine if this is an effect of the antibody on the clearance and distribution of galsulfase or interference of the antibody with the ELISA, resulting in apparently lower plasma concentrations and thus higher clearance.

Two of the three subjects, 026-002 and 024-005, had 77% and 80% reductions from baseline at Week 24 in urinary GAGs, respectively, indicating that the effect of galsulfase was not impaired and supporting the hypothesis that the antibody is interfering with the ELISA. In contrast, subject 024-003 had a smaller urinary GAG reduction from baseline (45%) compared to the other patients in the PK cohort (average reduction from baseline of 75%), suggesting that antibody is potentially impacting galsulfase distribution and uptake. On the other hand, if instead of considering the baseline urinary GAG, we take as baseline the Week 1 urinary GAG level, this subject had a similar reduction in urinary GAG (75%) as the rest of the group, corroborating the suspicion of an effect of antibodies on the ELISA measurements of galsulfase.

### 5.1.4 Study XO-001

The purpose of this study was to demonstrate pharmacokinetic and pharmacodynamic equivalence between the clinical (lot produced using a — , in the clinical facility) and commercial (lot produced using — in the commercial facility) materials in subjects who had received galsulfase treatment for an extended period of time. After 179 to 188 weeks of galsulfase treatment, the four subjects in the Phase 1/2 study 00-01 were transitioned to the commercial process galsulfase. Similarly, the ten subjects in Study 01-04 transitioned to commercial process galsulfase between Week 98 and 117 of treatment.

The mean values for $C_{max}$, $AUC_{0-t}$ and $AUC_{\infty}$ were comparable between the commercial and clinical materials. The 90% confidence intervals for the geometric mean ratios for $C_{max}$ and $AUC_{0-t}$, commercial-to-clinical, for which N = 14, were within the 80% to 125% equivalence windows. The geometric mean ratio for $AUC_{\infty}$, which could be estimated for both treatments for

10 of 14 patients, was 109% and the upper limit of the confidence interval was > 125%. However, the two process products were also equivalent with respect to urinary GAG levels (77.8 ± 34.8 and 77.5 ± 40.1 µg/mg creatinine, clinical and commercial, respectively), with a mean ratio of essentially 100% and a 90% confidence interval of 84% to 115%, indicating equivalent pharmacodynamics. Based on $C_{max}$, $AUC_{0-t}$ and urinary GAGs, the clinical and commercial materials were equivalent. At worst, there was a possible 9% increase in $AUC_{\infty}$ with the commercial material.

## 5.2 Pharmacodynamics

The pharmacodynamic endpoint that can be clinically assessed and is common to MPS VI and other mucopolysaccharidoses is the urinary excretion of GAGs. Under normal circumstances, lysosomal N-acetylgalactosamine 4-sulfatase or arylsulfatase B catabolizes dermatan sulfate, and this effect is reflected in the urinary excretion of normal amounts of GAGs. Patients with MPS VI excrete higher levels of GAGs, generally 2 – 10 times higher than normal.
During all clinical studies in the development of galsulfase, there has been consistent reduction of urinary GAGs in those subjects treated with galsulfase. The effect was seen within 4 – 6 weeks from the onset of treatment and near maximum reductions were seen between weeks 6 and 8. The effect was consistent across studies and was persistent over time. The between-groups difference in urinary GAG reduction in the Phase 3 study 03-05 was significant, with a 73 % reduction in subjects treated with galsulfase as compared to placebo. Though it is important to note that urinary GAGs levels did not normalized in any of the subjects, some subjects nearly reached the upper limit of normal for urinary GAGs excretion.

## 5.3 Exposure-Response Relationships

One limitation of this product development was the lack of exploration of multiple doses and dose regimens. The dosing regimens employed in the Phase 2 and Phase 3 studies were extrapolated from animal studies, particularly the feline model of MPS VI. For details, please refer to Section 3.2 of this review, Animal Pharmacology / Toxicology. The Phase 1 / 2 study 00-01 was an attempt to evaluate 2 doses of galsulfase for a period of 24 weeks in only 7 subjects. Since one of the subjects withdrew from the study after the 3rd infusion, and was not assessed for any efficacy endpoints post-baseline, a comparison can only be made between the 3 subjects randomized to the 0.2 mg / kg dose vs. 3 subjects randomized to the 1 mg / kg galsulfase dose. Both doses caused significant reductions in urinary GAGs. Subjects exposed to the lower dose had decreases of –71, - 43 and – 50 % from baseline to Week 24; the reduction in the 3 subjects treated with 1 mg/ kg was – 52, - 79 and – 79 %. The reduction in dermatan sulfate (the direct substrate for this enzyme) was parallel to that observed for urinary GAGs. The decline in urinary GAGs appeared to be more rapid among those treated in the higher dose cohort. Thus, there was a suggestion of increased efficacy among the subjects receiving the higher dose, but the sample is very small, and no firm conclusion regarding a dose-response is possible.

# 6 INTEGRATED REVIEW OF EFFICACY

The integrated review of efficacy described in this section is based on the single Phase 3 study (ASB-03-05) and its open-label extension (ASB-03-06). Study ASB-03-05, entitled "A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter, Multinational Clinical Study of Recombinant Human N-acetylgalactosamine 4-sulfatase (rhASB) in patients with Mucopolysaccharidosis VI" provides the primary evidence of efficacy. Its goal was to evaluate the ability of galsulfase to enhance endurance in subjects with MPS VI, as evidenced by an increase in the number of meters walked in the 12-minute walk test (12 MWT) at Week 24 compared to baseline. A secondary goal stated was to evaluate the ability of galsulfase to reduce urinary GAG levels at Week 24. The open-label extension study (ASB-03-06) provides supportive evidence of efficacy, in that subjects who were assigned to placebo in the controlled study were switched to active treatment. (Subjects remained blinded to treatment assignment in the original study.) Thus, for these subjects, it is possible to compare treatment responses before and after galsulfase was initiated. Additional studies that provide support for the efficacy of galsulfase in the treatment of patients with MPS VI are described in the appendix, in Section 9 of the review document.

## 6.1 Indication

The indication being sought is: NAGLAZYME is indicated for patients with MPS VI. NAGLAZYME has been shown to improve walking and stair climbing capacity." The indication contains no limits as to demographic subsets, disease severity, characteristics of the gene defects or functional impairment of ASB in the affected patients.
*Reviewer comment: The indication statement is reasonable, and consistent with prior agreements reached with BioMarin.*

### 6.1.1 Methods

The efficacy review is based on the data obtained from Study 03-05 and its extension study 03-06. As will be extensively discussed under section 6.1.4 below, the evidence of galsulfase efficacy comes from the combined data obtained from study 03-05 and its extension 03-06. The efficacy data from the extension Study 03-06 were submitted by BioMarin at the request of FDA, following discussion during the Pre-BLA meeting that occurred on September 28, 2004. BioMarin submitted only the efficacy data from the first 24 weeks into that ongoing extension study.

### 6.1.2 General Discussion of Endpoints

MPS VI is a rare condition, with a wide spectrum of disease severity and heterogeneous rate of progression to fatal outcomes. These features of MPS VI make a large study, with robust endpoints such as rates of survival unfeasible. Examination of the literature cases published as

well as those described in the Online Mendelian Inheritance in Man (OMIM) database indicate that most patients are affected to varying degrees in their respiratory capacity, joint function and locomotion, and in their cardiovascular function. The cause of death in patients with MPS VI is frequently associated with complications of the restrictive airway disease, cardiomyopathy or cardiac valvulopathy.

- The primary efficacy endpoint was the distance walked in a 12-minute walk test (12 MWT). The selection of the 12 MWT as the primary endpoint for demonstration of efficacy came from a pre-Phase 3 agreement with the FDA. This endpoint is based on the ability of the 12 MWT to provide a direct functional measure of the limitations in the activities relevant to daily living of patients with MPS VI, but also an indirect measure of the combined cardiovascular, respiratory and articular capacity of each particular patient. Although the wide spectrum of presentations would preclude a choice of either one of the 3 systems (cardiovascular, respiratory or articular) as representative of the entire group, the 12 MWT represents an integration of the 3 systems, even as the magnitude of impairment within a particular system is very different among patients. The distance walked in the 12 MWT is a clinical endpoint, and is not viewed by FDA as a surrogate for clinical benefits in terms of substantial morbidity or mortality.

  The review of the laronidase BLA provided a precedent in accepting a walk test as a measure to demonstrate the efficacy of enzyme replacement therapy in MPS I, a disorder of mucopolysaccharide accumulation similar to MPS VI. In that product development, the two co-primary endpoints were a change in the distance walked in 6 minutes from baseline to Week 26 and the change in the predicted forced vital capacity from baseline to Week 26. FDA had asked the Advisory committee in charge of the independent evaluation of laronidase about the appropriateness of the 6-minute walk test in that application, and the panel members recommended acceptance of the endpoint and considered the product efficacious for MPS I based, in part, on these results.

  Furthermore, BioMarin conducted a survey study (ASB-00-02) in which 121 patients with MPS VI were enrolled. That study consisted of a one time visit to evaluate the range and diversity of clinical presentations of patients with MPS VI. The study findings supported the selection of an endurance measure as affecting the majority of patients with MPS VI, across all age groups. The survey revealed that some patients had severe respiratory impairment and sleep apnea, but with low prevalence that would not yield substantial evidence of efficacy in that endpoint in a controlled study.

  The walk test was performed once to screen for eligibility prior to enrollment (subjects were not told the qualifying distance) and twice, on separate days at baseline, Weeks 6, 12, 18, 24 of the double blind placebo controlled study and at Weeks 36 and 48 (counting from baseline) in the open label extension study. The subjects were told to walk as far as possible, and during the test, they were notified when they reached the 6- and the 12-minute timepoints. Blind subjects could use a string as a guide. No assist device was allowed. Heart rate and oxygen saturation (the latter assessed with pulse oximeter) were monitored before the start of the test, immediately after completion and 2 minutes following completion. A stopwatch was used to time the test and the same location was used for all tests at each site.

- The secondary efficacy endpoints are the number of stairs climbed in a 3-minute stair climb test and the urinary GAGs level as a function of creatinine excretion. The 3-minute stair climb test has been used in screening patients being considered for lung surgery, as a tool for cardiovascular surgery risk assessment and for evaluation of certain arthritis patients (please refer to Section 11. References). The references we were able to gather from the recent literature and the references provided by BioMarin do not point to a standardized method of conducting the study. The references indicate that the stair climb test is an assessment of endurance, and indirectly, an assessment of respiratory capacity. It was initially listed as a tertiary endpoint, but at the request of the FDA, was elevated to a secondary efficacy endpoint in an amendment dated 8/1/03. In addition, FDA recommended alternative analyses if more than 10 % of climbs achieved the top of the stairs within the allowed 3 minutes time for the test. The robustness of the results would then be explored by comparing the rate of climbing (number of stairs climbed / number of minutes in the climb) and other comparisons as sensitivity analyses. It is unclear what, if any, differences exist between the assessment of stair climbing and the walk test, as both generally cover the endurance and respiratory capacity of the subjects tested. Also unclear during the planning of this study and in the planning of the Phase 2 study 01-04 was the within-patient correlation between distance walked in 12 minutes and number of stairs climbed. The test was performed twice (on separate days), at baseline, Weeks 6, 12, 18, and 24 of the double-blind, placebo controlled study 03-05 and at Weeks 36 and 48 (counting from baseline) during the extension study 03-06. The stairs had a railing the subject could use for support. The same stairs were used for all the evaluations conducted at each site. Subjects were told they could stop climbing at any time and rest, but no verbal encouragement or physical assistance could be given at any time during the test. Like in the 12 MWT, heart rate and oxygen saturation (through pulse oximeter) were monitored prior to initiation of stair climb, at completion, and 2 minutes after completion. The four endurance tests (two 12-MWT and two Stair Climb tests) were never performed on the same day.

  Urinary GAGs were included as a secondary measure of efficacy by BioMarin. FDA made several comments about this endpoint to BioMarin in pre-Phase 3 discussions. FDA noted that urinary GAGs are a pharmacodynamic endpoint, and not a clinical endpoint indicative of benefit to patients with MPS VI. The correlation between urinary GAG levels at baseline and the severity of disease in different systems and organs was poor. Urinary GAG level was the only secondary endpoint proposed in the original protocol. Urinary GAGs were measured twice at baseline (on separate days), and once at Weeks 1, 4, 8, 12, and 24 of Study 03-05 and at Weeks 36 and 48 during the extension study 03-06. Urinary GAGs were measured in the first voided urine sample in the morning, prior to study drug infusion, using an [redacted] procedure.

Tertiary endpoints for the controlled part of the study (Study 03-05) included:

- the shoulder range of motion, which was to be assessed by active and passive flexion, extension, and lateral rotation, measured with a goniometer, preferably by the same person at every visit. Further explanation from BioMarin on this endpoint is as follows: the primary outcome of interest is the average of left and right shoulder active flexion among the subset of subjects whose baseline range of motion is less than 90 degrees, and in this subset, the

endpoint is a binary variable, improvement by at least 10 degrees in the average shoulder range of motion. The other motions (passive flexion, active and passive extension and active and passive lateral rotation) are exploratory outcomes.

- a coin pick up test as a measure of dexterity and sensation, in which subjects are asked to pick up 50 coins, one by one, in 1 minute, without scooping coins to the side of the table. The number of coins is recorded, and if subjects pick up all 50 coins in less than 1 minute, the total time elapsed is recorded.
- joint pain and stiffness and physical energy level based on assessments made using a visual analog scale.
- visual acuity, as assessed by Snellen charts (because of a substantial number of missing measurements at baseline, this endpoint was not included in the data analysis plan).

Tertiary endpoints for the extension study (Study 03-06) included:

- cardiac function, as assessed by echocardiogram.
- respiratory function, as assessed by pulmonary function tests using spirometry. In the subjects with tracheostomy, standard spirometry was to be performed if the subject could tolerate temporary occlusion of the tracheostomy.
- health resource utilization, by recording antibiotic use, hospitalizations, days missed from work or school, requirements for wheel chair or other ambulatory aid, requirement for positive airway pressure during sleep, and other parameters.
- visual examination, as assessed by visual acuity as well as an ophthalmologic examination (intra-ocular pressure, cornea examination for clouding, retina / optic nerve examination.

*Reviewer comment: BioMarin and FDA had discussed the use of these endpoints for the Phase 3 study and agreed on their appropriateness to both detect a treatment effect and adequately represent the spectrum of clinical benefit for patients with MPS VI. Given the wide variability of presentation and progression of MPS VI, a single endpoint would be unlikely to represent an improvement for the majority of these patients. FDA had requested that BioMarin include assessments of pulmonary and cardiovascular function during the 24 weeks of the controlled study, but BioMarin replied that in the very small subject population in this study and with many having tracheostomies, demonstration of clinical and statistical benefits would be extremely difficult. In addition, BioMarin would expect that any benefit would only be made evident after the 24 weeks of the planned controlled study, during the extension.*

### 6.1.3 Study Design

#### 6.1.3.1 Protocol:

The original protocol for Study 03-05, entitled "A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter, Multinational Clinical Study of Recombinant Human N-acetylgalactosamine 4-sulfatase (rhASB) in patients with Mucopolysaccharidosis VI" was submitted on May 13, 2003. The original protocol for Study 03-06, entitled "A Multicenter,

Multinational Open Label Extension Study of Recombinant Human N-acetylgalactosamine-4-sulfatase (rhASB) in Patients with Mucopolysaccharidosis VI" was submitted on December 10, 2003.

6.1.3.2 Background

Study 03-05 was designed based on the results obtained in the pre-clinical studies in culture fibroblasts, feline MPS VI model, as well as the first 96 weeks of the Phase 1 Study 00-01 (including a double-blind, dose controlled period and a single arm open label extension) and the first 24 weeks of the Phase 2 Study 01-04. Based on these studies, BioMarin concluded that galsulfase treatment resulted in improvement in endurance and urinary GAG excretion by 24 weeks, as well as some improvement in shoulder range of motion and joint pain. In addition, the choice of endpoints and the range of severity in endurance parameters allowed for entry were chosen based on a survey of 121 patients with MPS VI (Survey Study 00-02). The selected dose to be tested in the study was derived from Study ASB-PC-00-02, conducted in newborn felines affected by feline MPS VI. In that study, newborn cats received weekly doses of recombinant human galsulfase at 0.2, 1.0 or 5.0 mg/kg over a 5- to 11-month period. The 5 mg /kg dose was clearly better in not only reducing GAG from liver Kupfer cells (the only benefit demonstrable at the 0.2 mg / kg dose level), but also by providing greater flexibility, less spinal cord compression, increased bone mineral density, as well as GAG clearance from heart valve, aorta, skin, dura, liver cells and brain perivascular cells. A study conducted in ~ laboratory, compared the 5 mg / kg dose of recombinant human enzyme administered to 3 cats to the 1 mg / kg of the recombinant feline enzyme administered to 2 cats over a period of up to 170 days, and conclude that the magnitude of pharmacodynamic effect of the 1 mg / kg of feline enzyme was equivalent to that of the 5 mg / kg of human enzyme in the BioMarin study. BioMarin concluded that if using homologous (same species) galsulfase, the magnitude of the pharmacodynamic effect is greatest with 1 mg / kg. Thus, the dose-controlled study, which was the opportunity to determine the best dose to use in efficacy studies, only included the 0.2 and 1 mg / kg doses of recombinant human galsulfase.

6.1.3.3 Goals:

The stated goal of the study was to evaluate the ability of galsulfase versus placebo to enhance endurance in patients with MPS VI as evidenced by an increase in the number of meters walked in the 12 MWT at Week 24 compared to baseline. A secondary goal stated was to evaluate the ability of galsulfase versus placebo to reduce GAGs excretion in patients with MPS VI at Week 24 compared to placebo. The goal of the extension study 03-06 was to evaluate the long-term efficacy and safety of galsulfase treatment in patients with MPS VI.

6.1.3.4 Design:

Study 03-05 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational study. The study was planned to enroll 36 subjects with MPS VI, randomized 1:1 to placebo or galsulfase. Subjects were planned to receive infusions of galsulfase 1 mg / kg over 4 hours on a weekly basis, or indistinguishable placebo. All subjects being considered for the study would undergo a 1- to 2-week period of screening, a 2-week period for baseline assessments, and then undergo randomization to either treatment group. The double-blind,

controlled treatment phase was designed to last 24 weeks, after which all subjects would be offered participation in an open-label, uncontrolled study. The extension study, 03-06, was designed to enroll subjects who had participated and completed study 03-05, to be treated with galsulfase from Week 25 until Week 240, unless the study is terminated or galsulfase receives marketing approval. Therefore, at the time of this review, study 03-06 is ongoing.

6.1.3.5 Eligibility:

Eligible subjects must:

- have been diagnosed with MPS VI (clinical signs and symptoms and documented fibroblast or leukocyte ASB enzyme activity level less than 10 % of the lower limit of normal)
- be able to walk between 5 and 270 meters in the first 6 minutes of a screening 12 minute walk test
- be able to walk $\leq 400$ meters in 12 minutes (per study amendment of 8/12/2003)
- have negative pregnancy test
- not be pregnant or lactating
- not have received bone marrow or stem cell transplantation
- not have clinically significant spinal cord compression.

For Study 03-06, the subject was eligible if he / she completed Study 03-05 with at least 20 of the 24 scheduled weekly infusions of study agent, having missed no more than 2 consecutive infusions and, in the case of a female subject, if not pregnant or lactating.

6.1.3.6 Randomization:

Eligible subjects were to be randomized in blocks to either galsulfase or placebo, stratified by site of treatment. The first 2 blocks at each site had 2 subjects and subsequent blocks had 4 subjects each.

6.1.3.7 Blinding:

BioMarin staff and the study sites had no knowledge of the block sizes for randomization. The randomization list was prepared by Statistics Collaborative and unblinding could only occur if deemed necessary by the BioMarin medical monitor. No unblinding was needed during the 24 weeks of Study 03-05. Furthermore, after the initial results of Study 03-05 were communicated to FDA, FDA requested that BioMarin not unblind subjects, families, or investigators for at least 6 months following enrollment into the Extension Study 03-06. BioMarin followed FDA's advice and maintained the blind on the treatment allocation under Study 03-05 for the initial 6 months, when all subjects knew they would be receiving treatment with galsulfase. In order to minimize unblinding related to infusion reactions, BioMarin determined that all subjects would be pre-treated with diphenhydramine or an equivalent anti-histamine.

6.1.3.8 Treatment:

Subjects received treatment with weekly intravenous infusions of either galsulfase 1 mg / kg or placebo. Infusions were administered over a 4-hour period. The minimum interval between infusions was 4 days. A study center pharmacist diluted the volume necessary for the weight-based dose of study drug in 250 mL of saline. The infusion rate was adjusted so that 2.5 % of the total volume was infused during the first hour, and the remainder (97.5 %) in three hours. Vital signs were monitored at least every 30 minutes for the first hour and hourly until completion of the infusion. All subjects are pre-treated with IV or PO diphenhydramine (up to 1.25 mg / kg, not to exceed 50 mg) or equivalent anti histamine. A central IV catheter was placed if there were difficulties with IV access. During the Extension Study 03-06 subjects have been allowed to receive treatment infusions at sites closer to their homes.

6.1.3.9 Monitoring:

Vital signs, weight, health resources utilization, adverse events and concomitant medications were assessed every week. Urinary GAG's, pregnancy test, anti-galsulfase IgG, complement, hematology, chemistry and urinalysis, shoulder range of motion, coin pick up, analog scales for assessment of joint stiffness, joint pain and physical energy, were assessed every 6 weeks. The endurance tests, 12-minute walk test and the 3-minute stair climb test were also assessed every 6 weeks, but were conducted twice in separate days for each timepoint. Respiratory function and visual examinations were conducted only at baseline and at Week 24. Echocardiogram and electrocardiogram were monitored at baseline and then only during the extension study 03-06.

6.1.3.10 Endpoints:

The primary endpoint was the distance walked in the 12 MWT. Secondary endpoints included the rate of stair climbing and urinary GAGs levels. Please refer to the listing and discussion of study efficacy endpoints under section 6.1.2, above.

6.1.3.11 Statistical plan:

*Study Population*: The population for all efficacy analyses consists of all randomized subjects. The only exception is analysis of shoulder flexion range of motion, to be tested only in the subset of subjects with limitations in this motion to less than 90 degrees at baseline.

*Sample size:* The sample size was estimated based on the standard deviation of the change in distance walked in the 12 MWT in study 01-04, which was approximately 150 meters. If the assumption of the same standard deviation applied to this Study 03-05, then 18 subjects per treatment group would yield 80 % power to detect a between group difference of 135 meters in the 12 MWT, under an analysis of variance test with baseline walk distance as the only covariate, with a type I error of 0.05 two-sided.

*Efficacy analyses:* The statistical analytical plan proposed in the original protocol described the primary efficacy analysis as a comparison between the change in number of meters walked in the 12 MWT from baseline to Week 24 between the treatment groups using an analysis of variance with baseline number of meters walked as the only covariate. In October 2003, BioMarin

submitted the revised statistical analytical plan, after receiving comments and agreement from FDA regarding the primary analysis of the efficacy endpoint changing from an analysis of variance to a longitudinal model with repeated measures that would take into account all timepoints in the study. The primary efficacy outcome was the number of meters walked in 12 minutes at Week 24 adjusted for baseline number of meters, as an increase in mean distance relative to placebo in the test, compared to baseline.

The longitudinal model had the following conditions: the method was a repeated-measures model stratified by site, used baseline walk distance as a continuous covariate, entered the time of measurement in the model as a categorical variable, assumed a compound symmetry covariance structure, and included a time by treatment interaction. The goal of the change in analysis method was to reduce variability in response by using repeated measurements on each subject, therefore adding information and increasing the power to detect a treatment effect for galsulfase, greater than the 80 % predicted for the analysis of variance. The longitudinal repeated measures analysis also allowed for addition of site as covariate, without spending degrees of freedom in this limited population. The plan called for underlying assumptions (e.g., normality of the residuals) to be tested and other exploratory analyses to be used if data showed assumptions were violated.

The same statistical analytical method was used for the stair climb test, a secondary efficacy endpoint. BioMarin has incorporated FDA's advice to take into account the possibility that a proportion of subjects will be able reach the top of the staircase within the 3 minutes of the test. Therefore the analysis became conditioned as follows: if less than 10 % of stair climbs reached the top of the staircase, the analysis would use the total number of stairs in the staircase; if more than 10 % of stair climbs reached the top of the staircase, sensitivity analyses would then be used to explore the robustness of results: rate of stair climb overall (i.e., the number of stairs climbed divided by the number of minutes in the climb) versus the number of stairs climbed in the first half plus the number of stairs extrapolated to 3 minutes at the rate of the second half of the climb, the latter assuming a non-constant rate of climbing. Other sensitivity analyses were planned as well.

The urinary GAGs between treatment would be tested with an analysis of variance of Week 24 urinary GAGs data to compare the treatment groups, stratified by site and using baseline urinary GAGs as a continuous covariate. BioMarin also planned to conduct a responder analysis, with a threshold for response being a $\geq$ 50 % reduction in urinary GAGs from baseline to Week 24. The supportive analysis to compare the proportion of "responders" would be performed using a Mantel-Haenszel test stratified by site.

*Missing data:* The handling of missing data was to follow pre-determined rules:

- For individual subject data, missing baseline values would be replaced by screening values if they were measured within 2 weeks of baseline. If no baseline or screening value was obtained, that subject was excluded from the analysis of that variable.
- A subject who discontinued the study after the first administration of study agent would be considered a treatment failure, and the imputation of his/her change from baseline data in the ITT analysis would follow the trajectory of the placebo group (the missing post-baseline

values would be imputed as the intercept adjusted for baseline plus the visit effects of the placebo group from the longitudinal modeling).

- Data from the last visit after Week 17 would be used to impute missing data on Week 24.
- Other sensitivity analysis were described to test the robustness of these methods to impute and handle missing data.

*Quality assurance:* The case report forms were reviewed manually at the study center for completeness by a BioMarin clinical monitor. Upon completion of all data entry, the database received a quality assurance check to ensure accuracy and completeness. The final statistical analytical plan was submitted prior to the locking of the database and unblinding the randomization codes.

6.1.3.12 Amendments:

Two amendments were introduced to the protocol for Study 03-05. Only the changes considered relevant are listed here:

Amendment 1 (August 1, 2003) was proposed to change some of the assessments made at baseline to screening and vice-versa, to define a limit for the distance walked at 12 minutes to 400 meters (in addition to that limit established for the first 6 minutes of the test at 270 meters) and to include corneal photographs and forced inspiratory vital capacity as a part of the respiratory function test.

Amendment 2 (August 25, 2003) was proposed to add respiratory function assessments and corneal examinations and photographs at the Week 24 timepoint.

6.1.3.13 Revisions to the Statistical Analytical Plan:

The statistical plan was amended in April 2004 to modify the analysis of the secondary endpoint 3 minute stair climb test from an analysis of variance to a longitudinal model using repeated measures, similar to the analysis of the primary endpoint. A responder analysis with establishment of a threshold was introduced in the same amendment for analysis of the reduction in urinary GAG.

Another change was made after the locking of the database and before unblinding, as follows: if the 2 distances walked at the Week 24 timepoint differed by more than 120 meters, the staff of Statistics Collaborative would look at the investigator's comments related to the explanation for the difference: if the comment described a pre-existing condition at the time of the walk which should have precluded the test on that day, the distance observed that day would be deleted and only the other distance walked would be computed for the Week 24 for analysis. Three subjects had a difference between their 2 distances walked on Week 24 greater than 120 meters, but from these only one subject who was ill (subject 21-006), had that day's distance excluded from the analysis.

6.1.3.14 Study Conduct:

The study was conducted under IND 9057. The case report forms were reviewed manually at the investigator site for completeness by a BioMarin clinical monitor and were returned to BioMarin for data management and analysis. The study center was contacted for any corrections or clarifications. All data were entered into a study database for analysis and reporting. Data that were captured electronically (for example, laboratory results), were transferred electronically directly to the database. Statistics Collaborative audited all programs it wrote. Each table in the report has a pathname that identifies the program that produced it.

Three contract research organizations were involved in the study: [redacted] (responsible for lab supplies and specimen management for testing at central labs as well as shipment of study drug to the sites), [redacted] responsible for data entry, data maintenance, and generation of study listings, and after the database lock, transferring the data to [redacted], and [redacted] (responsible for generation of the randomization schema, coordination of randomization with the IVRS, statistical analysis of the data, generation of summary tables and figures, and statistical interpretation of results).

An independent Allergic Reaction Review Board was established to review severe or serious infusion associated reactions during the study, and served as consultant to the clinical team and medical monitor. The members of the Board were physicians not involved in the study, and at least one member was an allergist / immunologist.

The report does not specify the dates of the database lock and the initiation of the statistical analysis. However, based on the flowchart of the interaction between the contract research organizations, it appears the database lock was not violated prior to unblinding and data analysis.

## 6.1.4 Efficacy Findings

6.1.4.1 Disposition:

Study 03-05 was initiated on July 21, 2003, (first consent signed) and ended on April 8, 2004 (last assessment performed). Study 03-06 started on February 9, 2004, and the current report for this BLA submission contains data through September 29, 2004. Forty-eight subjects were screened and 39 subjects were enrolled at 6 sites in Study 03-05. Most of the screen failures were related to either complete inability to walk or walking distance in excess of the limits established for eligibility.
The clinical sites were:

- Children's Hospital and Research Center in Oakland CA (Dr. Paul Harmatz)
- University of Mainz in Germany (Dr. Michael Beck)
- Royal Manchester Children's Hospital, in England (Dr. James Wraith)

After completion of the assessments for Study 03-05, the subjects who opted to continue participation in Study 03-06 (all subjects did) could receive galsulfase treatment and certain protocol-specified assessments at a site near their homes, after approval from the BioMarin medical monitor, the principal investigator for the site, and the local IRB. All efficacy evaluations in the extension study 03-06 were performed at the 6 original sites.

Of the 39 subjects enrolled, 36 had been participants in the Survey Study 00-02. Table 7 shows the distribution of subjects according to site and treatment allocation.

**Table 7. Subject disposition by treatment group and site in Study 03-05**

| Site | Group | | Total (N=39) |
|---|---|---|---|
| | Galsulfase (N=19) | Placebo (N=20 | |
| | n (%) | n (%) | n (%) |
| USA | 2 (11) | 4 (20) | 6 (15) |
| Germany | 4 (21) | 4 (20) | 8 (21) |
| England | 3 (16) | 3 (15) | 6 (15) |
| Brazil | 4 (21) | 4 (20) | 8 (21) |
| France | 2 (11) | 3 (15) | 5 (13) |
| Portugal | 4 (21) | 2 (10) | 6 (15) |

Subject 20-006 who had been randomized to placebo, withdrew consent after receiving the infusion at Week 5, and missed the first post-baseline assessments at Week 6. His data were imputed according to the plans for imputation of missing data described in the statistical analytical plan. All other subjects completed Study 03-05 and enrolled in Study 03-06.

6.1.4.2 Protocol Violations:

*Eligibility:* Of the 39 subjects enrolled in the study, 11 (8 subsequently randomized to placebo and 3 to galsulfase) did not fulfill eligibility requirements and were granted exceptions to participate in Study 03-05. Of the 11 protocol violations of the eligibility criteria, 7 were related to excessive walking distances, between 400 and 600 meters in 12 minutes (5 on placebo and 2 on galsulfase), 3 were related to age being less than 7 years at the time of randomization and 1 was an 18 year old subject who had a bone marrow transplantation at age 7 with no engraftment observed.

*Monitoring:* A number of subjects did not have visual acuity assessments at baseline, and some of the centers did not use protocol-specified methods for assessment of visual acuity, so the effect of galsulfase on visual acuity could not be evaluated in the study.

*Treatment:* A small number of infusions were scheduled outside the weekly limits proposed in the protocol. A small number of doses were calculated on the basis of current weights at the time of the visit instead of weight assessed monthly, as directed in the protocol.

6.1.4.3 FDA site inspection findings:

Three sites were inspected by FDA:

In the Oakland, California site, three discrepancies relating to reporting adverse events for the same subject (18-005) were noted. These AE's were present in the medical chart and were absent in the Case Report Forms. These AE's were minor (nasal congestion, mild leg pain, and a positive PPD in separate visits), and did not affect the conclusions of the overall safety and efficacy of galsulfase in this review.

The Mainz, Germany site was found to have several protocol violations: lack of use of an analog scale to rate physical energy level, lack of assessments of joint pain and stiffness at some timepoints, lack of vital signs monitoring during a few of the infusions in each of the subjects whose records were reviewed, and some elements of the informed consent form were missing.

The Manchester, England site was also found to have several protocol violations: lack of use of an analog scale to rate physical energy level, missing assessments of joint pain and stiffness at some timepoints, and missing elements of some of the informed consent forms. In addition, complement testing was performed on site for subject 002 at Week 1 post-baseline, and for all subjects during Week 6, without notification from the sponsor. This could result in some unblinding; however FDA found no evidence for biased outcomes in these subjects.

6.1.4.4 Demographics:

Gender and race were well distributed between treatment groups. Two-thirds of the subjects were female. The majority of subjects were white and non-Hispanic, which may reflect the predominance of this racial group in the regions of the globe where the study took place as well as access to appropriate diagnosis and health care.

6.1.4.5 Baseline characteristics:

On average, galsulfase-treated subjects were 3 years older than placebo-treated subjects (mean ages of 13.7 versus 10.7 years, respectively). This is a potentially important difference, given the relatively young ages of the subjects, and given that this phase of life may be characterized by extensive changes in physical endurance in MPS VI patients. Specifically, for normal adolescents, there are profound developmental changes during this period, with marked improvement in endurance. For MPS VI patients, there may be fewer developmental changes; in fact, endurance could be adversely affected by progression of the disease. Given these unknowns, the difference in age has the potential to confound interpretation of the study. Height and weight also tended to be higher in the galsulfase group, consistent with the difference in age.

All subjects had coarsened facial features, macrocephaly and macroglossia, similar to the features described in the literature on MPS VI. All subjects had reported valve disease by history. BioMarin did not provide in the clinical report any details on the cardiovascular findings that lead to the checking off "history of valve disease" in the Case Report Forms. This reviewer looked into the electrocardiographic and echocardiographic findings and noted a variety of valve abnormalities without any specific valve predominance and without stenotic / regurgitant predominance, and a wide spectrum of trans-valve gradients observed. One interesting finding was that none of the echocardiographic findings observed at baseline for the subjects enrolled in Site 18 (Oakland) were considered to be clinically significant, whereas in other sites either the majority or the totality of echocardiographic findings were considered clinically significant.

All subjects had musculoskeletal symptoms, such as joint stiffness, pain, contractures and spinal deformities. Sleep apnea was found in 23 of the 39 subjects, being 11 in the galsulfase group and 12 in the placebo group at baseline. Pulmonary hypertension, restrictive lung disease were present in approximately equal proportions in the 2 groups, as was history of pneumonia (a little over 50% in each group). Hepatomegaly was present in 34 of the 39 subjects, similarly distributed between the 2 groups. Forty-nine (49 %) had neurologic symptoms, including seizures, communicating hydrocephalus, cervical instability and myelopathy, and spinal cord and peripheral nerve compression.

The endogenous ASB enzyme activity was very low or undetectable in all subjects in Study 03-05. Although the assay was different in different sites and differed as to whether the ASB activity was measured in leukocytes or in skin fibroblasts, the most frequent method used was that of Karageorgos (Karageorgos, 2004, Human Mutation). The normal range for the method used is 11.8 to 39.4 pmol/min/mg, as determined in more than 60 subjects. Of note, enzyme activity and concentration were measured and reported in subjects in studies 00-01 and 01-04, and BioMarin concluded that there was a poor correlation between ASB activity and severity of clinical manifestations in the 7 subjects of Study 00-01 and the 10 subjects in Study 01-04.

**Table 8. Demographic and baseline disease characteristics of subjects in Study 03-05 per treatment group**

| Characteristic at baseline | | Galsulfase (n=19) | Placebo (n = 20) |
|---|---|---|---|
| Gender (count) | Female | 12 | 14 |
| | Male | 7 | 6 |
| Age (years) | Mean (± SD) | 13.7 (± 6.5) | 10.7 (± 4.3) |
| Race / Ethnicity (count) | White | 15 | 9 |
| | Hispanic | 1 | 3 |
| | Black | 1 | 2 |
| | Asian | 1 | 1 |
| | Indigenous | 1 | 1 |
| | Other | 0 | 4 |
| Height (cm) | Standing (Mean ± SD) | 104.4 ± 12.9 | 100.3 ± 13.5 |
| | Sitting (Mean ± SD) | 57.0 ± 14.1 | 55.8 ± 11.2 |
| Weight (kg) | Mean (± SD) | 24.6 (± 9.1) | 20.8 (± 7.9) |
| Important MPS VI features (count) | Coarse facial features | 19 | 20 |
| | Macrocephaly | 17 | 16 |
| | Macroglossia | 17 | 19 |
| | Corneal clouding | 19 | 19 |
| | Valve disease | 19 | 20 |
| | Left heart failure | 2 | 0 |
| | Sleep apnea | 11 | 12 |
| | Pulmonary hypertension | 4 | 3 |
| | Restrictive lung disease | 14 | 13 |
| | Hepatomegaly | 17 | 17 |
| | Splenomegaly | 16 | 15 |
| | Joint stiffness / pain | 19 / 16 | 17 / 17 |
| | Cervical myelopathy | 2 | 1 |
| | Communicating hydrocephalus | 3 | 3 |
| ASB enzyme in fibroblasts | Mean Activity (pmol/min/mg) ± SD | 0.077 ± 0.087 (n = 13) | 0.087 ± 0.110 (n = 14) |
| | % of LLN | 0.7 % | 0.7 % |

6.1.4.6 Efficacy endpoints:

*6.1.4.6.1 Distance walked in the 12-minute walk test*

**6.1.4.6.1.1 Baseline distance walked**

Table 9 shows the distance walked (mean ± SD) in the 12 MWT according to treatment groups at baseline. In addition to the intent-to-treat dataset of 39 subjects, BioMarin created 2 additional datasets, related to violation of the entry criteria for distance walked. The 32 subjects who fulfilled the walking eligibility criteria constitute the "Walk Eligible" dataset, and the 28 subjects who walked less than 400 meters at baseline constitute the "≤ 400 meter" dataset.

**Table 9. Distance walked in the 12 MWT at baseline by treatment group**

| Dataset | Galsulfase | | Placebo | |
|---|---|---|---|---|
| | n | Mean ± SD (meters) | n | Mean ± SD (meters) |
| ITT | 19 | 227 ± 170 | 20 | 381 ± 202 |
| Walk eligible | 17 | 197 ± 146 | 15 | 329 ± 199 |
| ≤ 400 meter | 16 | 170 ± 110 | 12 | 243 ± 125 |

There was a significant imbalance at baseline with respect to the mean distances walked by the galsulfase and the placebo groups. There were 5 exceptions granted to the distance criterion for subjects that were subsequently randomized to placebo, and 2 exceptions granted to subjects who subsequently were randomized to galsulfase treatment. Even when not considering these subjects, the walk eligible dataset still demonstrates the same magnitude of imbalance between groups. The further analysis of the ≤ 400 meter subset aimed to exclude from the analysis those 3 subjects randomized to placebo and the single subject randomized to galsulfase who, despite having met the limits of eligibility in reference to their screening walking distance, walked further than the allowed 400 meter at baseline. Even in that subset the difference was substantial.

**6.1.4.6.1.2 Distance walked in the 12-Minute Walk test over both studies 03-05 and 03-06**

The mean (± SD) improvement in distance walked from baseline to Week 24 (end of the controlled study 03-05) was 109 ± 154 meters for the galsulfase group and 26 ± 122 meters for the placebo group. The estimated difference between the groups in the changes in distance walked from baseline to Week 24 was 83 ± 45 meters. Between Weeks 24 and 48 (endurance data reported in this application) the mean (± SD) increase in distance walked in the galsulfase group was 36 ± 97 meters, a small increase above the increase noted in controlled study, whereas the placebo group experienced an increase of 66 ± 133 meters in the 24 weeks in which the group received galsulfase.

Table 10 and Figure 1 show the changes in the mean 12 MWT distances (± SD) over the 24 weeks of Study 03-05, as well as the distance walked in Weeks 36 and 48 of the extension study 03-06.

**Table 10. Distances walked in the 12 MWT over time in studies 03-05 and 03-06, by treatment groups**

| Timepoint | Galsulfase | | Placebo | | Difference (Mean ± SE) |
|---|---|---|---|---|---|
| | n | Mean ± SD (meters) | n | Mean ± SD (meters) | |
| Baseline | 19 | 227 ± 170 | 20 | 381 ± 202 | -154 ± 60 |
| Week 6 | 19 | 290 ± 201 | 19 | 383 ± 213 | - 93 ± 67 |
| Week 12 | 19 | 303 ± 216 | 19 | 398 ± 208 | - 94 ± 69 |
| Week 18 | 18 | 344 ± 202 | 19 | 399 ± 226 | - 55± 70 |
| Week 24 | 19 | 336 ± 227 | 19 | 399 ± 217 | - 63± 72 |
| Week 36 | 18 | 341 ± 235 | 18 | 447 ± 227 | * |
| Week 48 | 18 | 372 ± 240 | 18 | 482 ± 206 | * |

*At Week 36 and 48 all subjects were treated with galsulfase in an open label manner.

Although the mean difference between groups decreased over time during Study 03-05, it persisted in being substantial at the end of the controlled study. Individual plots of subjects in both treatment groups with their baseline (week 0) and Week 24 distances walked in the 12 MWT are shown in Figure 1:

Figure 1. Individual plots of distances walked in the 12 MWT at baseline and at Week 24 in Study 03-05 by treatment group

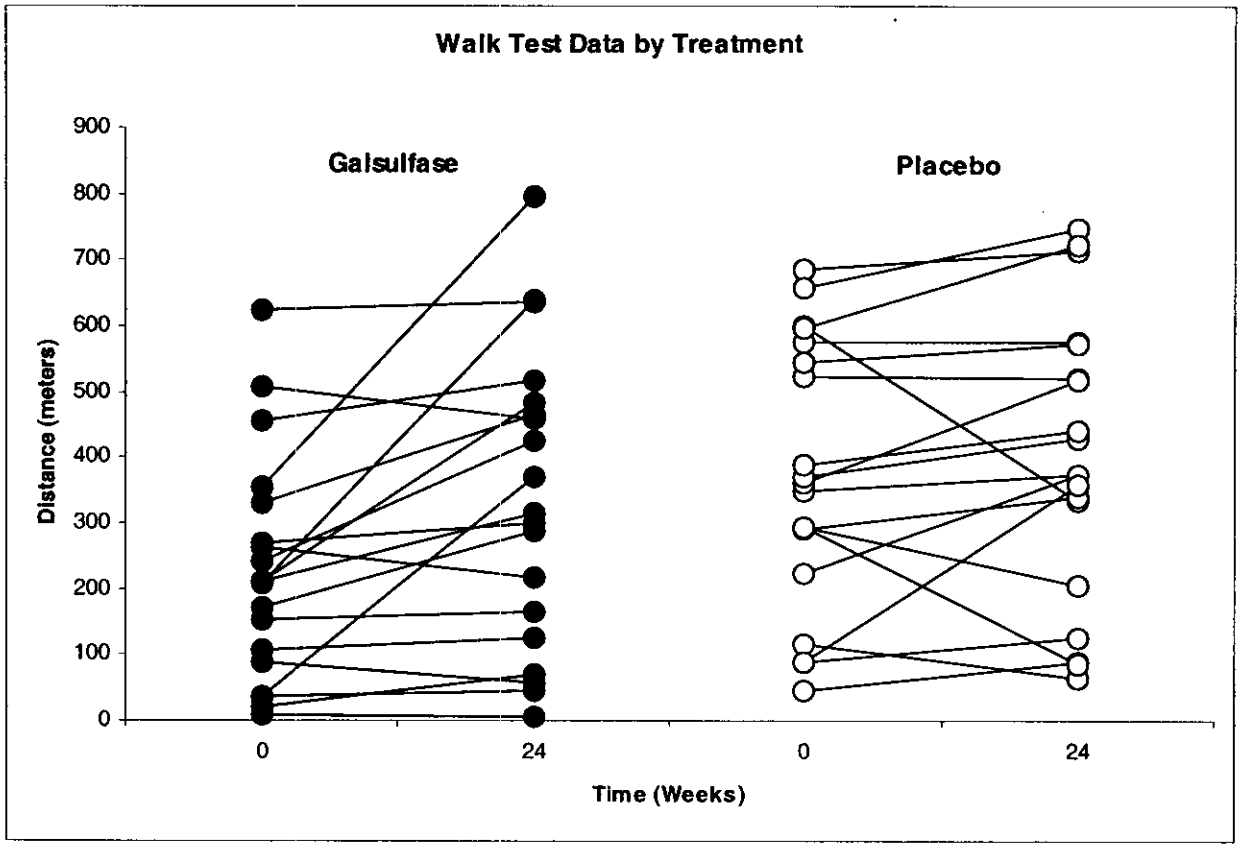



Figure 1 does not shown the individual variation over time, which was substantial from one visit to the next, and instead highlights the groups heterogeneity. A few galsulfase subjects demonstrated substantial improvements, whereas a few had slight worsening in the distances walked from baseline to Week 24. A few placebo–treated subjects demonstrated improvements in the distances walked over time, but two had very substantial decreases between baseline and Week 24.

Figure 2 shows the mean (± SD) distances walked in the 12 MWT as measured every 6 weeks during Study 03-05 and every 12 weeks in the extension Study 03-06, where all subjects were treated with galsulfase.

**Figure 2. Mean 12 MWT distances walked over time in Studies 03-05 and 03-06, by treatment groups**

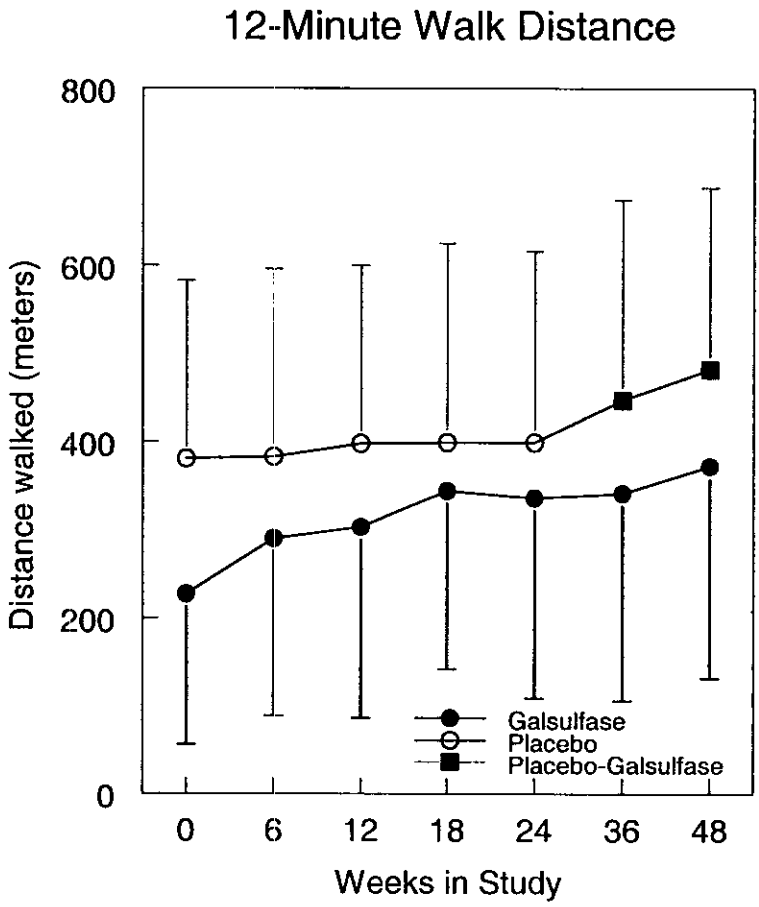



Figure 2 shows the striking imbalance between treatment groups at baseline, as well as the wide variability between individual subjects. The mean 12 MWT distance remained essentially unchanged in placebo subjects over the first 24 weeks of the study, whereas subjects treated with galsulfase improved their 12 MWT distance by roughly 50 % through Weeks 18 and 24. After Week 24, subjects in the original placebo group were switched to active treatment. Importantly, these subjects exhibited apparent improvement in 12 MWT distance at Weeks 36 and 48, relative to their "baseline," during Weeks 0 through 24, supporting a galsulfase treatment effect.

The substantial imbalance in baseline distance walked makes interpretation of the magnitude of treatment effect difficult. Although 12 minute walk distance improved in the galsulfase group, mean distance remained less than the mean baseline distance in the control group. *In other words, the apparent treatment effect of galsulfase was less than the baseline imbalance.* A discussion on the interpretability of the treatment effect of galsulfase follows below:

As suggested by the wide standard deviation, there was substantial overlap between groups for subjects' distances. At baseline, subjects randomized to placebo were able to walk longer distances than those randomized to galsulfase. On average, they were also younger and shorter than those randomized to galsulfase. Because the gender was well balanced between the groups, it could not provide a plausible explanation of the imbalance in baseline distance. Because ASB

activity < 10 % of normal was a criterion for study inclusion, mean ASB activity was low in both groups, and the values were not substantially imbalanced.

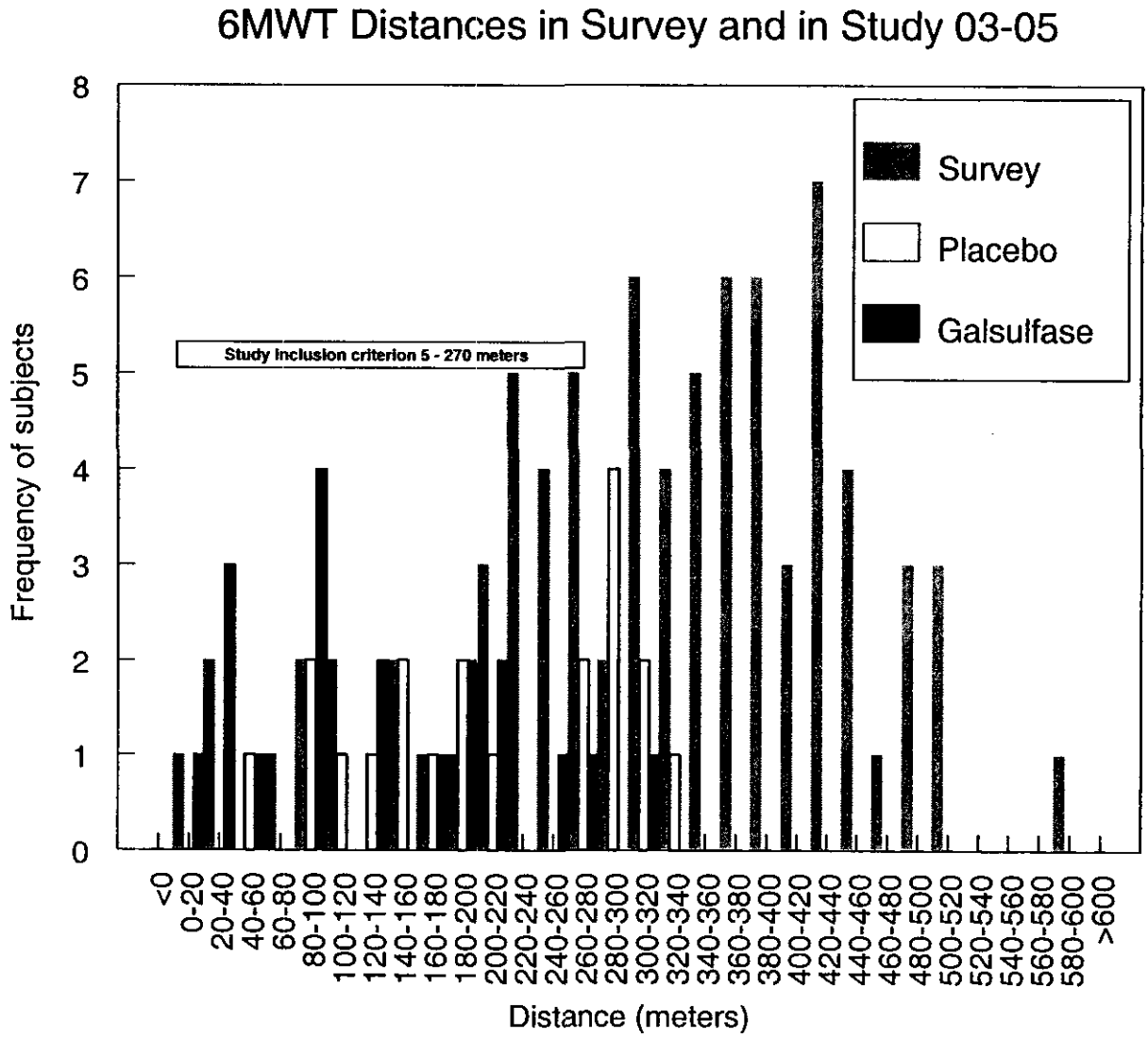
A possible explanation is that older subjects are exposed to the deteriorating effects of MPS VI for a longer period of time, and therefore had more severe disease, consistent with the shorter distance walked in the 12 MWT. If this is the case, age would have a negative influence over the distance walked. However, the data suggest only a weak correlation between age and severity of disease.

The randomization process appeared adequate, such that the imbalance would seem to be related to play of chance.

Another factor, the inclusion in the study of 5 subjects who could walk more than 400 meters at 12 minutes during screening who were eventually randomized to placebo and only 2 exceptions for the same reason being allowed to participate in the study being randomized subsequently to galsulfase, accounts for only some of this imbalance. As seen on Table 9 excluding these 7 subjects from the analysis still maintains a large difference between the groups.

To better illustrate how this sample of 39 subjects selected for Study 03-05 compares to the wider MPS VI population, as observed in the Survey study 00-02, please refer to Figure 3

**Figure 3. Distance in the 6-minute walk test in subjects during the Survey and at baseline of Study 03-05**

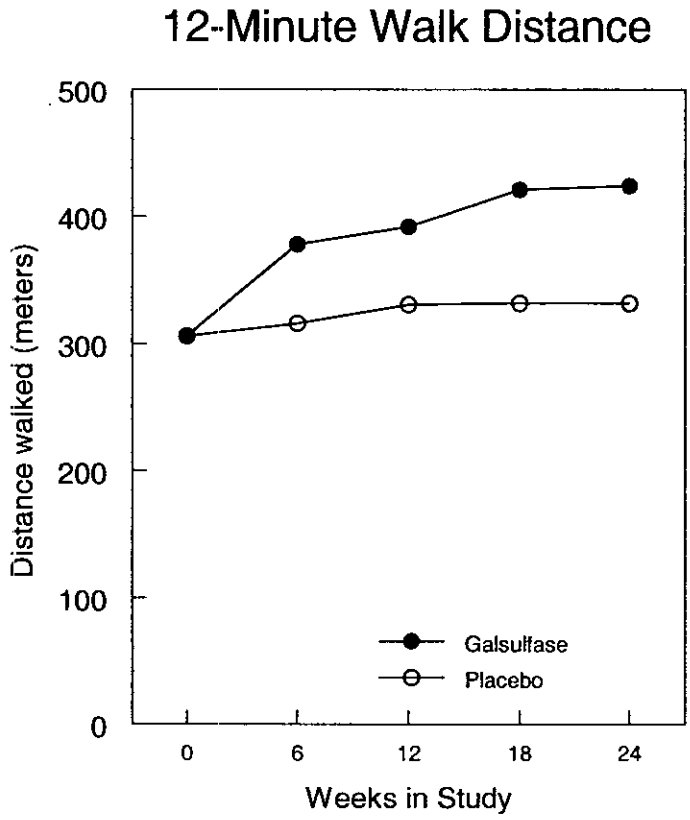



Compared to the survey subjects, note that the eligibility criterion on baseline walking distance selected subjects at the lower end of the spectrum of walking distances, and that the majority of patients with MPS VI in the survey could walk between 240 and 520 meters in 6 minutes. Although not being representative of the larger group in the survey, the stricter entry criteria regarding distance walked in 6 and in 12 minutes for the subjects for Study 03-05 was justified due to the need to demonstrate a treatment effect within the constraints of the study: a single study, in a rare population, that needed to be conducted in a controlled fashion through only 24 weeks. The figure also shows the distribution of subjects in study 03-05, according to treatment group, with higher frequency of subjects with greater distances allocated to placebo and greater frequency of subjects with lower distances walked allocated to galsulfase.

In view of the difficulty interpreting the 6 MWT results due to the baseline imbalance, BioMarin conducted a series of sensitivity / exploratory analyses to verify the robustness of the treatment effect. One analysis deserves particular attention and commentary, since BioMarin proposed to

introduce the data resulting from this analysis in the label for galsulfase. This analysis was an adjustment for the baseline imbalance in distance walked at the 12 minute test by assigning a weighted average of the means of the galsulfase and the placebo groups to each group, where the sample size in each group defines the weight. Then the longitudinal model adjusted the means as differences from the common baseline in each group. This process depicts the results no differently than in Figure 2, with a common baseline being the exception. Figure 4 shows the changes in mean distances walked by the 2 groups over time, during Study 03-05, as adjusted to a common baseline of 306 meters.

**Figure 4. Mean distances walked in the 12 MWT by treatment group, adjusted for a common baseline**

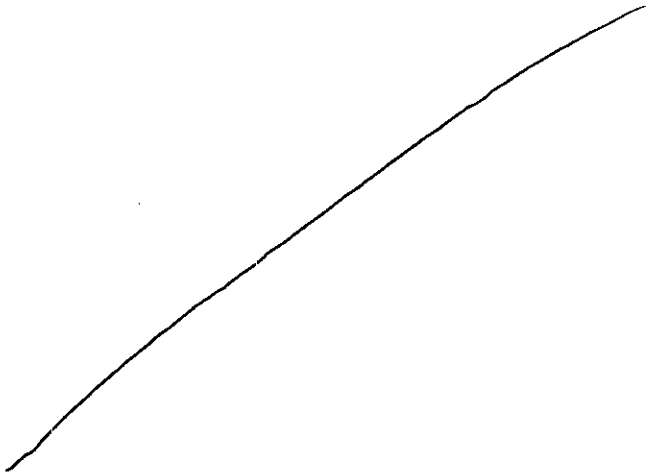



According to the longitudinal model used in the analysis of these data, the estimated difference between galsulfase and placebo in the 12 minute walk test at Week 24 was 92 ± 40 (mean ± SD) meters, with a 95 % CI of 11 – 172 meters (Table 11).

**Table 11. 12 MWT Data observed and adjusted for baseline in Study 03-05**

| | Observed (raw) Data | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | rhASB | | | Placebo | | | Difference | |
| | n | Mean | SD | n | Mean | SD | Mean | SE |
| Baseline | 19 | 227 | 170 | 20 | 381 | 202 | –154 | 60 |
| Week 6 | 19 | 290 | 201 | 19 | 383 | 213 | –93 | 67 |
| Week 12 | 19 | 303 | 216 | 19 | 398 | 208 | –94 | 69 |
| Week 18 | 18[2] | 344 | 202 | 19 | 399 | 226 | –55 | 70 |
| Week 24 | 19 | 336 | 227 | 19 | 399 | 217 | –63 | 72 |
| | | | | | | | | |
| | Fitted (predicted) Data* | | | | | | | |
| | rhASB | | | Placebo | | | Difference | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI |
| Baseline | 306 | — | | 306 | — | | 0 | — |
| Week 6 | 378 | (322, 434) | | 316 | (263, 369) | | 62 | (–18, 142) |
| Week 12 | 392 | (336, 447) | | 331 | (278, 384) | | 61 | (–20, 141) |
| Week 18 | 421 | (365, 478) | | 332 | (279, 385) | | 89 | (9, 170) |
| Week 24 | 424 | (368, 480) | | 332 | (280, 385) | | 92 | (11, 172) |

The proposed labeling under this application inserts a Table under Clinical Studies with a summary of the walk distances at baseline and at Week 24 derived from this table, with the fitted (predicted data), as follows:



Thus, BioMarin attempted to analyze the data in such a way as to adjust for the imbalance at baseline. The sponsor has provided multiple sensitivity analyses, all pointing to a positive treatment effect, albeit at different magnitudes. This reviewer believes that there is a demonstrable treatment effect; however, its magnitude is difficult to quantify.

Other sensitivity analyses supplied by BioMarin in this application include the comparison of the change in distance walked in the 12-minute walk test among those walk-eligible (by removing the 7 subjects who were able to walk $\geq$ 400 meters at screening) and the "< 400 meter" subsets. Table 13 shows the changes from baseline to Week 24 in the 2 treatment groups and the estimated between-groups differences in these changes, for each subset analyzed.

**Table 13. Distances walked in the 12 minute walk test among different subsets of subjects in Study 03-05**

| Dataset | Galsulfase | | Placebo | | Estimated Mean ± SE Difference in change from baseline to Week 24 between galsulfase and placebo | | p-value for comparison of data as adjusted for baseline |
|---|---|---|---|---|---|---|---|
| | n | Mean change from baseline to Week 24 ± SD (meters) | n | Mean change from baseline to Week 24 ± SD (meters) | Based on raw data | Based on data adjusted for baseline | |
| ITT | 19 | 109 ± 154 | 20 | 26 ± 122 | 83 ± 45 | 92± 40* | 0.025 |
| Walk eligible | 17 | 113 ± 161 | 15 | 18 ± 134 | 95 ± 52 | 115±47* | 0.016 |
| ≤ 400 meter | 16 | 128 ± 160 | 12 | 41 ± 123 | 87 ± 53 | 118± 51 | 0.024 |

In the ITT population, as well as in the 2 subsets used in these sensitivity analyses, the between-groups differences in the 12-minute distance walked is statistically significant, using the longitudinal analysis model proposed by BioMarin.

One concern the FDA review team had was the possibility that the improvement seen within the galsulfase-treated group could be attributed to a "regression to the mean." Under this scenario, subjects randomly allocated to the galsulfase treatment group would have exhibited lower than expected endurance at baseline. A variety of causes could transiently reduce endurance, including increased joint pain, respiratory impairment, etc. The expected course of endurance over time, following the transient worsening, would be improvement. If most subjects assigned to placebo did not experience this deterioration in endurance prior to the baseline assessments, this would account for the differential effect seen between the groups. The data submitted in the application cannot completely dispel this concern. However, evidence for a true treatment effect can be made stronger from comparing the distance walked by all individuals at screening and at baseline. Subjects had their 12 MWT evaluations for screening and at baseline separated by several days to a few weeks. Table 14 below shows the summary statistics and the difference between baseline and screening distances for the 2 groups:

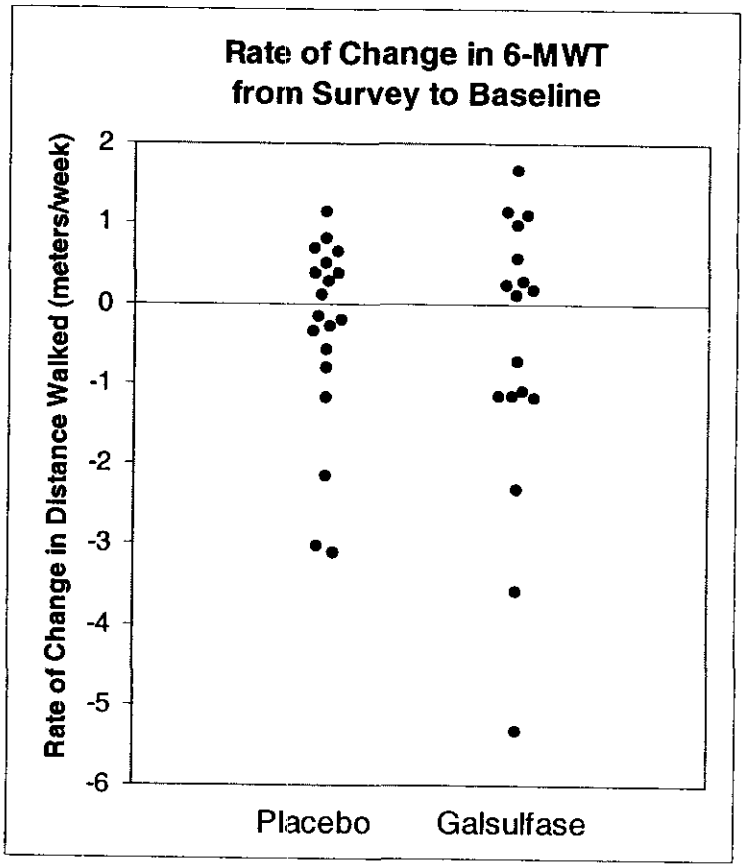
**Table 14. Mean distances walked in the 12 MWT at screening and at baseline for Study 03-05 by treatment group**

| Treatment Group | Mean Distance at Baseline (± SD) | Distance at Screening (± SD) | Mean (± SD) Difference of Distance: Baseline - Screening |
|---|---|---|---|
| Galsulfase | 227 (170) | 236 (184) | -9.5 (89.8) |
| Placebo | 381 (201) | 376 (174) | 5.0 (71.6) |

Distances walked in the 12-minute test were very consistent from screening to baseline in both treatment groups.

Another way to consider the possibility of regression to the mean is to compare the distances walked at 6 minutes during the survey with the distances walked in the first 6 minutes of the 12 MWT used for screening of subjects that participated in study 03-05. For galsulfase-treated subjects, lower distances walked at the time of screening compared to the distance walked at the time of the survey would suggest regression to the mean, particularly if such a trend was not evident in the placebo group. For the majority of subjects evaluated both at the survey and in study 03-05, these evaluations were separated by a 1- or 2-year period. Figure 5 shows the rate of change (meters of distance walked divided by weeks from the survey to the screening) for subjects who were both in the survey and in Study 03-05. Two subjects eventually randomized to galsulfase and 1 subject eventually randomized to placebo were excluded from this analysis. The considerable overlap between the 2 groups in the differences in distance walked from the Survey to screening of Study 03-05 does not support a regression to the mean explanation for the 12 MWT results (Figure 5).

**Figure 5. Slope of change in distances walked in the 6 MWT from the Survey to Screening of Study 03-05**

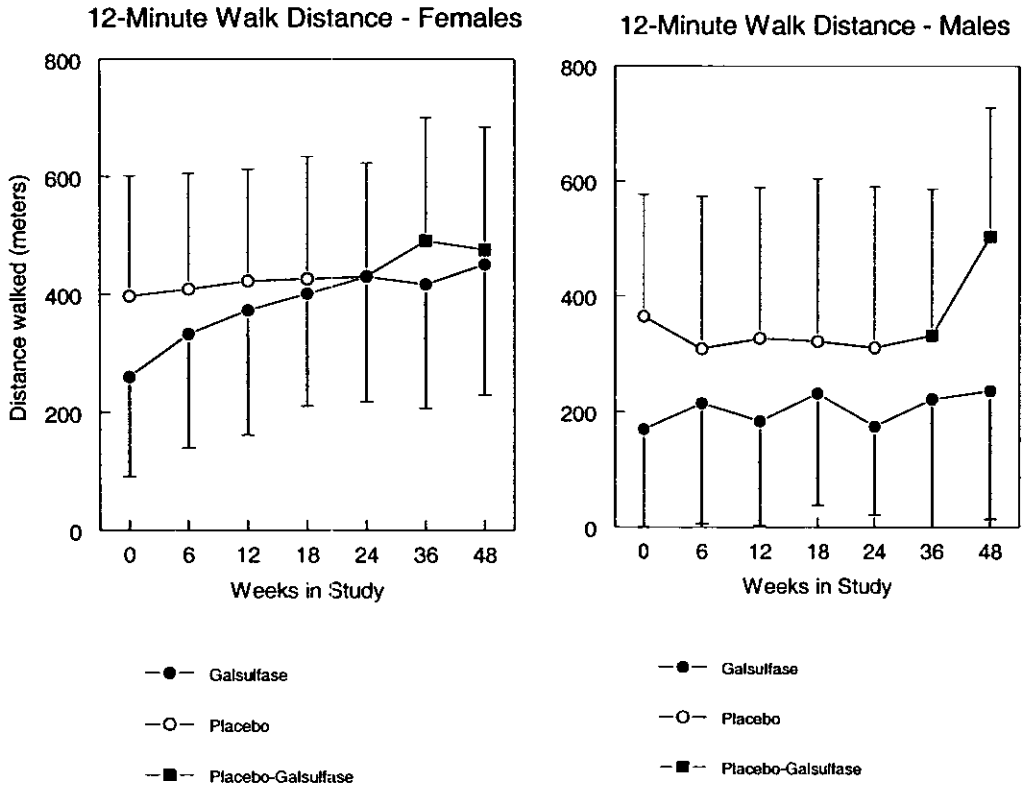


An alternative explanation for the results seen in Study 03-05 is a ceiling effect on the distance walked by the placebo group, wherein those subjects, as a group, could not be expected to exhibit further improvement in their endurance, as measured by the 12MWT. This is consistent with the concept that these somewhat younger placebo patients were not significantly impaired by their disease. However, the survey data argue otherwise (Figure 3). That is, the placebo group in study 03-05 demonstrated considerable impairment relative to the survey population, suggesting that there were, in fact, importantly affected by their disease. Thus, although this concern also cannot be completely dispelled, it seems unlikely. These concerns are significantly attenuated when we take into consideration the increase in distance walked by the placebo group during the extension phase, Study 03-06 (see data in Table 10 and Figure 2). It is noteworthy that all subjects participated in the first 24 weeks of the open label extension without being told their original treatment allocation in Study 03-05, reducing the potential for expectation bias. That is, subjects who had been receiving galsulfase in the extension phase, given knowledge that they had been on placebo previously, could experience an improvement in endurance. By not disclosing treatment assignment to these subjects, there was less potential for bias. The placebo group experienced a mean (± SD) increase in distance walked from the Week 24 (end of Study 03-05) to Week 48, after 24 weeks of active treatment, of 66 (± 133) meters. The range of increment in distance walked is similar to that observed in the galsulfase-treated subjects during the controlled study 03-05. Importantly, these data show an apparent treatment response in the original placebo, decreasing the concern that the placebo group had reached a ceiling at baseline and no further improvement could be expected.

### 6.1.4.6.1.3 Other analyses for the Primary Endpoint for the controlled study 03-05

Effect of Galsulfase by Gender

**Figure 6. 12 MWT in Studies 03-05 and 03-06 by gender**




During the 24 weeks of Study 03-05, both male and female galsulfase-treated subjects demonstrated improvement in distances walked in the 12 MWT, although the effect appears to be more pronounced and consistent over time in females than in males. Further improvement in distance walked can be seen also during the extension Study 03-06, albeit at smaller magnitude. For those subjects randomized to placebo, no changes can be seen during the controlled Study 03-05, but the distances walked in the 12 MWT improve in both genders once they receive galsulfase treatment during the extension study (Figure 6).

Effect of Galsulfase by Age Categories

For this analysis, the FDA reviewer divided the dataset into 3 subsets: those between the ages of 5 and 9 years of age, inclusive, named "Pre-pubertal", those between the ages of 10 and 14, inclusive named "Pubertal", and those between the ages of 15 to 29 years, named "Adult".

**Table 15. 12 MWT by age group in Study 03-05**

| Age Categories | Galsulfase | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Week 24 | Change | n | Baseline | Week 24 | Change |
| Pre-Pubertal | 7 | 300 ± 193 | 437 ± 126 | 137 | 9 | 361 ± 209 | 408 ± 189 | 47 |
| Pubertal | 5 | 252 ± 155 | 380 ± 214 | 128 | 7 | 406 ± 211 | 398 ± 237 | - 8 |
| Adult | 7 | 135 ± 132 | 203 ± 271 | 68 | 3 | 334 ± 243 | 376 ± 330 | 42 |

In galsulfase-treated subjects, there is a trend of longer distances walked at baseline for the younger age groups, as well as greater improvement in distance walked during treatment. These trends are not evident in the placebo subjects. Although the numbers of subjects in each subset are small, the data suggest that younger patients may be more responsive to the effects of galsulfase, with greater reversal of their physical impairment.

Effect of Galsulfase by impairment in endurance at baseline

The FDA reviewer divided the dataset in 3 tertiles, according to the mean distance walked in 12 minutes at baseline for the entire group of 39 subjects. Table 16 shows a summary of the changes in distance walked according to the endurance at baseline, measured by the 12 MWT.

**Table 16. 12 MWT by baseline distance walked in Study 03-05**

| **Distance walked at baseline (meters)** | **Galsulfase** | | | | **Placebo** | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Week 24 | Change | n | Baseline | Week 24 | Change |
| 9.2 - 208 | 9 | 93 ± 72 | 196 ± 205 | 103 | 4 | 85 ± 29 | 159 ± 134 | 74 |
| 210 - 360 | 7 | 269 ± 56 | 429 ± 189 | 160 | 6 | 302 ± 50 | 316 ± 150 | 14 |
| 369 - 685 | 3 | 529 ± 85 | 538 ± 89 | 8 | 10 | 547 ± 103 | 561 ± 146 | 13 |

This table shows that the tertile with the greatest distance walked at baseline had the least change over the course of Study 03-05.

It is not possible to differentiate the influence of the effect of age on the change in distance walked from the effect of gender, because there is also an association between the 2 demographic characteristics, as seen in Table 17:

**Table 17. Relation between age and gender among subjects in Study 03-05**

| Age categories | Females | Males |
|---|---|---|
| Pre-pubertal | 13 | 3 |
| Pubertal | 7 | 5 |
| Adult | 6 | 5 |
| Total | 26 | 13 |

Similarly, there is a relation between the gender distribution of the overall group and the magnitude of impairment in endurance at baseline, seen in Table 18.

**Table 18. Relation between gender and distance walked at baseline among subjects in Study 03-05**

| Distance walked at baseline | Females | Males |
|---|---|---|
| 9.2 – 208 | 7 | 6 |
| 210 – 360 | 9 | 3 |
| 369 - 685 | 10 | 4 |
| Total | 26 | 13 |

Effect of study site on the 12-minute walk test

The sensitivity analysis conducted by BioMarin on the treatment effect to inclusion of study site as a covariate is shown in Table 19, below:

**Table 19. Effect of study site in the 12 MWT in Study 03-05**

| Model | Estimate of treatment effect* | 95 % CI | p-value |
|---|---|---|---|
| Site as a covariate | 92 ± 40 | (11, 172) | 0.025 |
| Excluding site as a covariate | 78 ± 39 | (1, 155) | 0.047 |

* Comparing galsulfase to placebo at Week 24, adjusted for baseline

Another way of demonstrating the effect of site on the 12 MWT is by analysis of the data after exclusion of each site and looking at the estimated differences between groups, using the same longitudinal model with repeated measures proposed for the primary analysis. This analysis is shown in the table below:

**Table 20. Effect of site in the 12 MWT by exclusion of each site, one at a time, in Study 03-05**

| Population subset | n | Difference in changes: baseline to Week 24 | Statistically adjusted for baseline | p-value |
|---|---|---|---|---|
| Study Overall | Placebo 19*<br>Galsulfase 19 | 83 ± 45 | 92 ± 40 | 0.025 |
| Minus Oakland Site | Placebo 15<br>Galsulfase 17 | 99 ± 52 | 115 ± 45 | 0.012 |
| Minus Germany Site | Placebo 16*<br>Galsulfase 15 | 59 ± 45 | 62 ± 40 | 0.13 |
| Minus England Site | Placebo 16<br>Galsulfase 16 | 58 ± 50 | 65 ± 48 | 0.18 |
| Minus Brazil Site | Placebo 15<br>Galsulfase 15 | 111 ± 55 | 132 ± 52 | 0.013 |
| Minus France Site | Placebo 16<br>Galsulfase 17 | 82 ± 44 | 87 ± 37 | 0.022 |
| Minus Portugal Site | Placebo 17<br>Galsulfase 15 | 95 ± 50 | 94 ± 44 | 0.037 |

*Subject 20-006 from Germany, randomized to placebo, dropped out of the study after Week 5 and had no Week 24 assessments in the 12 MWT

In order to assess the importance of each study site in the overall results, the sponsor repeated the analysis of the primary endpoint using the longitudinal model with repeated measures, with omission of individual study sites. As noted in Table 20, exclusion of either site 20 (Germany) or Site 21 (England) yields between-groups differences that are smaller than individual exclusion of the other sites. Elimination of either the English or German site rendered the results not statistically significant; however, in a study of this size, this is neither surprising nor concerning.

Effect of galsulfase on the 12 minute walk test in other studies in MPS VI

Endurance, as measured by the 6-minute and/ or the 12-minute walk test, have been evaluated in studies 00-01 and 01-04.

Study 00-01 was a Phase 1, 24-week, dose controlled study of galsulfase: 0.2 mg / kg IV weekly (n=4); 1 mg / kg IV weekly (n=3). The study was succeeded by an ongoing open-label extension study, wherein all subjects are receiving galsulfase 1 mg / kg IV weekly. One of the study endpoints was the 6 MWT (Table 21). One subject randomized to 0.2 mg / kg discontinued study participation at Week 3, and had no post-randomization assessments of 6 MWT. Subject 50 withdrew from the study at Week 32.

**Table 21. Distances walked in 6 MWT in Study 00-01 and its extension**

| Patient ID | Dosage Group | Screening Distance (m) | Week 24 | | Week 48 | | Week 144 | |
|---|---|---|---|---|---|---|---|---|
| | | | Change in Meters from Screening \| % of Screening | | | | | |
| **41** | **0.2** | 196.7 | 16.3 | **+8%** | 7.5 | **+4%** | 92.2 | **+47%** |
| **45** | **0.2** | 283.1 | 42.1 | **+15%** | 125.3 | **+44%** | 114.6 | **+40%** |
| **50** | **0.2** | 133.0 | 9.6 | **+7%** | NAV | – | NAV | – |
| **42** | **1.0** | 388.1 | –32.7 | **-8%** | 19.7 | **+5%** | 235.8 | **+61%** |
| **43** | **1.0** | 53.1 | 99.3 | **+187%** | 125.8 | **+237%** | 122.7 | **+231%** |
| **44** | **1.0** | 88.7 | 62.7 | **+71%** | 37.4 | **+42%** | 3.6 | **+4%** |

The open-label extension of that study showed improvement in 4 of the 5 subjects ranging from 40 to 231 % of baseline (92 to 236 meters) at Week 144, and the 5th subject (Subject 44) had severe neurologic complications due to cervical spinal cord compression, and had no change at Week 144 compared to baseline, even though the same subject had a 71 % increase by Week 24.

Study 01-04 : In this study, open label galsulfase was administered weekly to 10 subjects with MPS VI for 48 weeks, as of the writing of the study report . Change at Week 48 ranged from +6 m to +237 m at 6 minutes (mean +91 m), and +47 m to +595 m at 12 minutes (mean ± SD was +211 ± 152 meters).

Even though these two studies were conducted with the subject's knowledge that they would be receiving active treatment, the fact that improvements in distance walked were shown for the majority of subjects is supportive of the data obtained in the Phase 3, adequately controlled study.

#### 6.1.4.6.1.4 Other sensitivity analyses

One post hoc change listed in amendment 1 of the Statistical Analytical plan of April 12, 2004, was submitted after locking the database, but before unblinding. Under that change, any subject whose 2 walk distances at Week 24 differed by more than 120 meters would have a blind review of the investigator's comments for that subject at that timepoint.

Subject 021-006 was ill at the time of the second 12 minute walk test at Week 24, and the datum from that day's test was excluded from analysis. The first test, conducted on February 24, 2004, demonstrated a 6-minute walked distance of 240 meters and 12-minute walked distance of 483 meters. The second test of Week 24, performed on February 26, 2004, showed both the 6-minute and 12-minute distances walked at 60 meters. If the walk data for that subject's second Week 24 test had been included, the mean ± SD for the galsulfase group would have been 325 ± 224 meters and the estimated difference in change from baseline to Week 24 between the groups would be revised from 92 ± 40 meters to 72 ± 37 meters (p= 0.052 in a model including site as a covariate or 0.059 in a model without the time by treatment interaction).

This reviewer investigated other examples in which there was a discrepancy between the two 12-minute walk distances assessed in a particular timepoint for all subjects in the Phase 3 study. Five subjects randomized to placebo and 3 subjects allocated to galsulfase had differences between day 1 and day 2 of the 12-minute walk test that were at least 200 meters apart, and whose data were included in the analysis because the subjects were in stable physical condition. Importantly to demonstrate minimization of intended or unintended bias is the fact that subject 024-002 had a near 500 meter difference in distance walked at Week 24, with many symptoms listed (hip pain, malaise, abdominal pain and diarrhea, hypotension), all of them with mild intensity, and the 2 distances were included in the analysis. This subject was treated with galsulfase. Other 2 subjects had discrepancies at Week 24, but no evidence of illness other than stable joint pain.

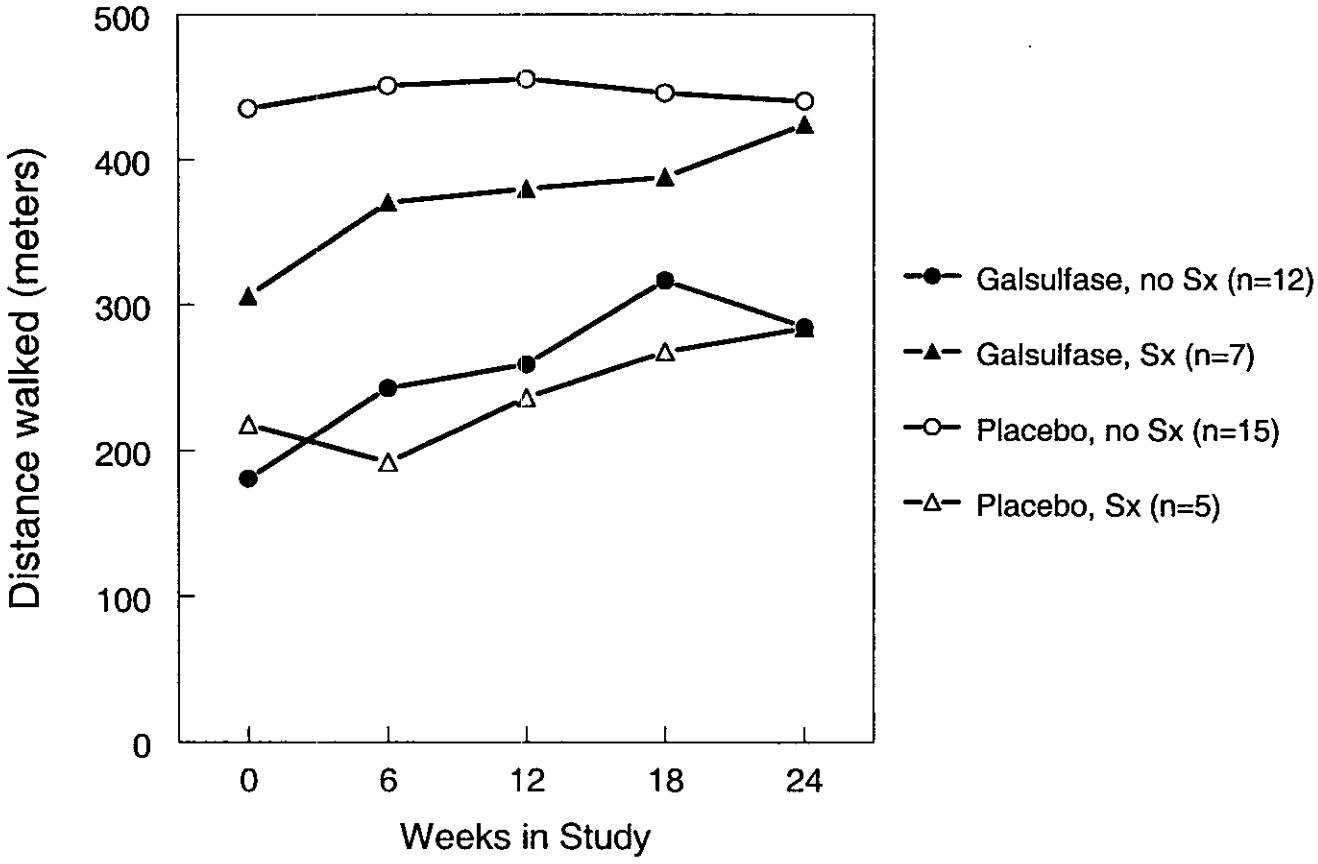
Other sensitivity analyses using longitudinal models yielded results with varying point estimates, but all showed beneficial effects of galsulfase in this endpoint. The inclusion of covariates (age, gender, height and their combinations) in the longitudinal model was also tested, and these analyses also resulted in point estimates between 62 and 92 meters of difference in changes from placebo, with p-values ranging from 0.016 to 0.13.

If BioMarin had used as the primary analysis of this efficacy endpoint the between-groups difference in change from baseline to week 24, the t-test would have shown a mean difference between groups of 85 ± 44 meters ($p = 0.062$). This analysis fails to consider intermediate timepoint data, however, data that provide a greater level of precision. In an analysis of variance that used only the baseline and Week 24 data, but included baseline distance walked as a covariate, the estimated difference in the change from baseline to Week 24 would have been 72 ± 48 meters ($p = 0.14$). Adding to this ANOVA model site as another covariate would increase the point estimate in the between groups difference to 103 ± 49 meters (95 % CI: 3, 204; $p = 0.044$).

BioMarin had also analyzed the 12-minute walk test data in a responder analysis, responder being described in the statistical plan as a subject who improved distance walked by ≥ 80 meters from baseline to Week 24. Using this definition, 8 subjects randomized to galsulfase and 5 to placebo were considered responders, with a Mantel-Haenszel odds ratio of 2.11 (95 % CI: 0.5 to 8.5, $p = 0.30$).

Another sensitivity analysis conducted by this reviewer was to explore the role of infusion reactions in the subjects' perception of unblinding (considering themselves as having been randomized to galsulfase) in Study 03-05 and the effect on the 12 MWT (Figure 7). For this analysis, the definition of "infusion reactions" was revised from BioMarin's definition of any AE's that were reported during infusions. Thirty-four AE's were excluded if they fell within these categories: IV infiltration, IV clotted, pruritus, tenderness, redness, or edema at the IV insertion site, and somnolence after receiving anti-histamines. These AE's were excluded because the reviewer consider them not sufficient to create a perception of treatment with the active drug ("unblinding").

**Figure 7. 12 MWT distances in Study 03-05 by presence or absence of infusion reactions**




* Sx: Symptoms related to infusion associated reactions.

Subjects treated with galsulfase who had an "infusion reaction" early in the course of the study were able to walk farther than those galsulfase-treated subjects who did not have "infusion reactions" or had them around Week 18 or later. The same is true for placebo-treated subjects who exhibited "infusion reactions", when compared to those placebo-treated subjects who did not have "infusion reactions". This would suggest a motivating effect of the perception of being treated with the active agent, a "placebo effect". However, the comparison of 12 MWT distances among the subjects treated with galsulfase and those treated with placebo who developed "infusion reactions" shows greater improvement from baseline in the 12 MWT among the galsulfase-treated than the placebo-treated subjects. Similarly among those subjects that did not have "infusion reactions", galsulfase-treated subjects did better than placebo-treated subjects. The conclusion is that a "placebo effect" exists based on the perception of unblinding caused by "infusion reactions", but despite the "placebo effect", a galsulfase treatment effect is seen.

A similar analysis was performed by examining the role of "infusion reactions" (same revised working definition used to plot Figure 7) only in subjects randomized to placebo in Study 03-05 who received galsulfase treatment between Weeks 24 and 48 in the extension Study 03-06 (Figure 8).

**Figure 8. 12 MWT distances walked by subjects randomized to placebo who were switched to galsulfase, by presence or absence of infusion reactions**

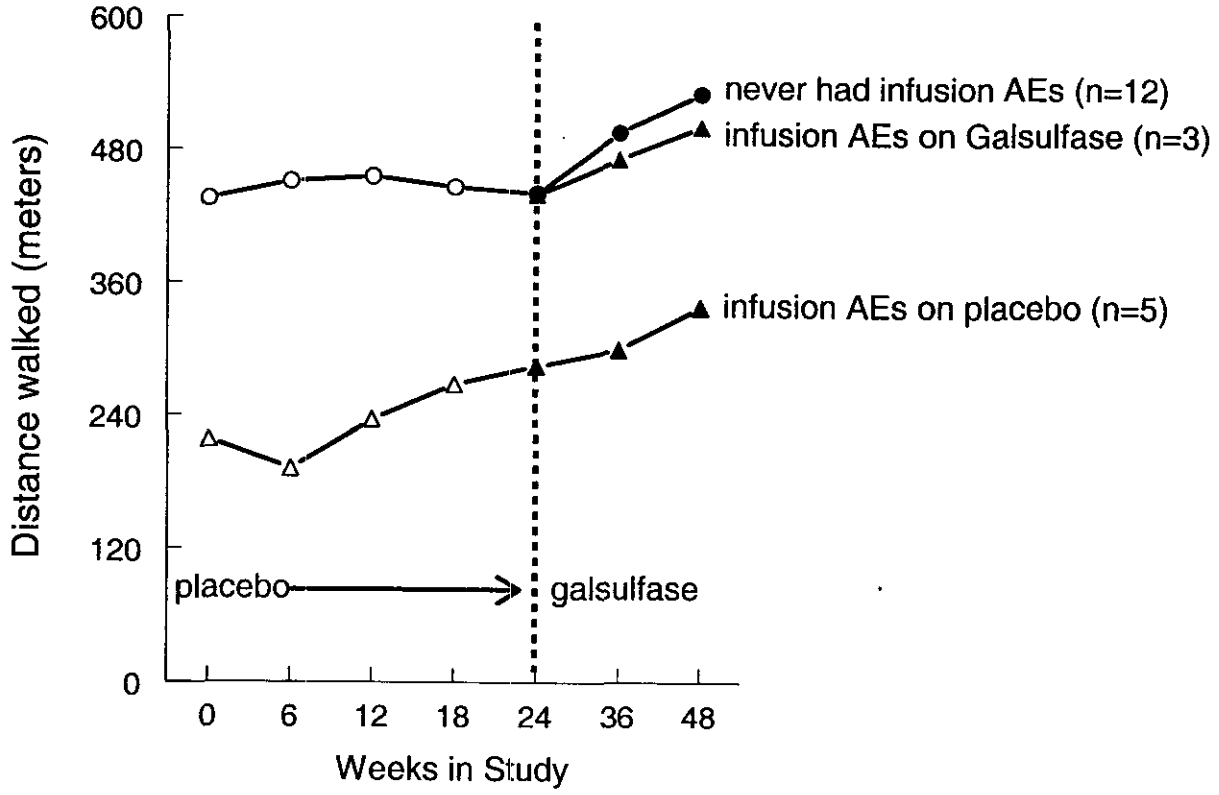



Figure 8 demonstrates that the increments in distance walked by the subjects originally randomized to placebo after being switched to galsulfase were virtually parallel, whether the subjects had "infusion reactions" while on placebo as well as on galsulfase, only after receiving galsulfase in Study 03-06 or whether they never had "infusion reactions". These data indicate that any potential expectation bias created by the perception of being treated with galsulfase (based on the presence of "infusion reactions") were not critical to the improvements of distances walked by placebo-treated subjects once they switched to galsulfase treatment in Study 03-06.

*Secondary efficacy endpoints:*

**6.1.4.6.1.5 3 Minute Stair Climb test:**

The statistical analytical plan related to this endpoint initially called for a comparison between treatment groups in the change over time in the number of stairs climbed in 3 minutes, unless > 10 % of the stair climbs reached the top of the staircase in less than 3 minutes. In the latter case, the rate of climb in the test would be the endpoint for comparing the treatment groups for this endpoint. Seventeen percent of all stair climbs in the study reached the top of the staircase, therefore the endpoint, according to the statistical analytical plan, was the **rate of stair climb**, rather than the **total number of stairs** climbed in 3 minutes. Out of the 439 stair climbs that did not reach the top of the staircase, 238 were climbed by subjects on active treatment and 201 by

placebo-treated subjects. Of the 87 stair climbs that reached the top of the staircase, 63 were climbed by placebo subjects and 24 by galsulfase-treated subjects.

For this endpoint, we see a substantial imbalance at baseline between the treatment groups, very similar to that seen in the 12 minute distance walked. The mean (± SD) 3-minute stair-climb rate at baseline for the galsulfase group was 19 (± 13) and for the placebo group was 31 (±18). As in the analysis of the primary endpoint, it is helpful and appropriate to display and analyze the combined results from Study 03-05 and its extension Study 03-06, regarding this endpoint.

Table 22 shows the 3-Minute stair climb rate over the 48 weeks of both studies 03-05 and 03-06:

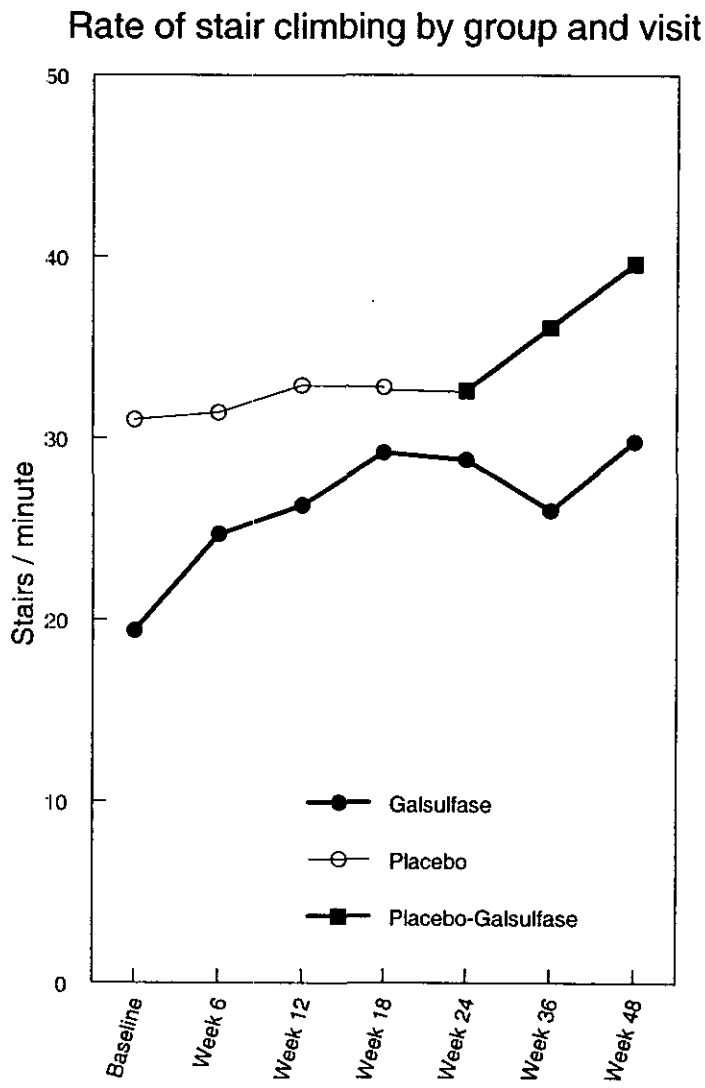
**Table 22. Rate of stairs climbed over time by treatment group in Studies 03-05 and 03-06**

| Timepoint | Galsulfase | | Placebo | |
|---|---|---|---|---|
| | n | Mean ± SD (stairs/min) | n | Mean ± SD (stairs/min) |
| Baseline | 19 | 19 ± 13 | 20 | 31 ± 18 |
| Week 6 | 19 | 25 ± 16 | 19 | 31 ± 20 |
| Week 12 | 19 | 26 ± 19 | 19 | 33 ± 20 |
| Week 18 | 18 | 29 ± 18 | 19 | 33 ± 20 |
| Week 24 | 19 | 27 ± 17 | 19 | 33 ± 20 |
| Week 36 | 18 | 26 ± 16 | 18 | 36 ± 21 |
| Week 48 | 18 | 30 ± 16 | 18 | 40 ± 19 |

From the longitudinal model proposed by BioMarin and accepted by FDA, the estimated difference between the mean change in rates among galsulfase- and placebo-treated subjects at Week 24 was 6 ± 3 stairs / minute ($p = 0.053$). In the walk eligible subset (those with a $\leq 270$ meters walked at 6 minutes and $\leq 400$ meters at 12 minutes at screening), the difference between groups at Week 24 adjusted for baseline in the rate of climbing was 7 stairs / minute ($p= 0.040$).

A graph of the rate of stair climbing in the 3-minute stair climb test across the study visits is depicted below, in Figure 9.

**Figure 9. Rate of stair climbing over time in Studies 03-05 and 03-06**




Another exploratory analysis of interest is the mean (± SD) number of stairs climbed in each visit by each treatment group, irrespective of reaching the top of the staircase. Table 23 below shows these data:

**Table 23. Number of stairs climbed in the 3-minute stair climb test, over time, in Studies 03-05 and 03-06**

| Timepoint | Galsulfase | | Placebo | |
|---|---|---|---|---|
| | n | Mean ± SD (stairs) | n | Mean ± SD (stairs) |
| Baseline | 19 | 58 ± 38 | 20 | 88 ± 49 |
| Week 6 | 19 | 74 ± 48 | 19 | 86 ± 49 |
| Week 12 | 19 | 73 ± 45 | 19 | 91 ± 52 |
| Week 18 | 18 | 85 ± 51 | 19 | 91 ± 51 |
| Week 24 | 19 | 79 ± 49 | 19 | 91 ± 50 |
| Week 36 | 18 | 77 ± 46 | 18 | 98 ± 49 |
| Week 48 | 18 | 87 ± 45 | 18 | 107 ± 44 |

In essence, these data parallel the rate of climb data. There is a considerable imbalance between treatment groups at baseline, with the mean number of stairs climbed by placebo group being approximately 50 % higher than that of the galsulfase group. During the 24 weeks of the controlled study, galsulfase-treated subjects increased their mean number of stairs climbed by 21 ± 29 stairs, whereas the placebo group increased by a mean 6 ± 20 stairs during the same period of time. Also similar to the data in the rate of climb, there was an increase in the mean number of stairs climbed by the placebo group (14 ± 24) stairs during the 24 weeks of open-label treatment with galsulfase, whereas the group continuing to receive galsulfase had a small additional increase of 8 ± 15 stairs.

Among those subjects who were in the walk eligible subset, the percent of stair climbs that had reached the top of the staircase was smaller, at 7 %. In that subset, the pre-specified primary analysis would be a comparison between the treatment groups of the number of stairs climbed in the 3-minute stair climb test. Within that subset, the difference in the mean number of stairs climbed between galsulfase and placebo groups was 21 ($p = 0.019$) at Week 24, adjusted for baseline.

In all sites except for Germany, the staircase remained the same through the study for all subjects. In Germany (site 20) the staircase was changed from a 140-stair staircase to a 206-stair staircase. For 5 of the subjects, the change occurred at Week 48 (week 24 of study 03-06), but 1 galsulfase-treated subject (020-003) was changed at Week 18 and one placebo-treated subject (020-008) was changed at Week 24. A brief comparison among the data obtained from the 140-stair staircase and those obtained from the 206-stair staircase does not indicate any bias that would lead to difficulty in interpretation of the results from that site or the study overall.

Correlation between the 12 MWT and 3 minute stair climb:

The correlations (expressed as $R^2$) between two endurance tests for both treatment groups are shown in Table 24, adapted from BioMarin's Table 7-1 in the application:

**Table 24. Correlation squared between the changes in the 12 MWT and the rate of stair climbing among treatment groups in Studies 03-05 and 03-06**

| Change between timepoints | Galsulfase | Placebo | Total |
|---|---|---|---|
| Week 24 - Baseline | 0.52 | 0.22 | 0.44 |
| Week 48 – Baseline | 0.59 | 0.09 | 0.44 |
| Week 48 – Week 24 | 0.29 | 0.59 | 0.49 |

The correlations between the endurance tests are not high, suggesting that these 2 endurance tests capture independent aspects of the disease, and the stair climb provides some confirmation of the beneficial effect as assessed by the 12 MWT.

Additional exploratory analyses of the 3 minute stair climb test:

*Analysis by gender*

Table 25 shows the effect of galsulfase on the 3 minute stair climb test by gender in the controlled study 03-05:

**Table 25. Rate of stair climb by gender in Study 03-05**

| Gender | Rate in Galsulfase (stairs/min) | | | | Rate in Placebo (stairs/min) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Week 24 | Change | n | Baseline | Week 24 | Change |
| Female | 12 | 23 ± 15 | 32 ± 19 | 9 | 14 | 31 ± 18 | 34 ± 19 | 3 |
| Male | 7 | 13 ± 6 | 18 ± 7 | 4 | 6 | 31 ± 21 | 28 ± 23 | 1 |

The major treatment effect in the galsulfase group was evident in female subjects with a mean increase from baseline to Week 24 that was more than twice as large as the increase observed in galsulfase-treated males. The data parallel the results of 12 MWT, where results were driven almost entirely by female subjects. Again, there was substantial imbalance in the rate of stair climbing at baseline.

Table 26 shows the changes in the rate of stair climbing, by gender and by treatment group, in the open-label extension study 03-06:

**Table 26. Rates of stair climbing by treatment group and gender: extension study 03-06**

| Gender | Rate in Galsulfase (stairs/min) | | | | Rate in Placebo/Galsulfase (stairs/min) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Week 24 | Week 48 | Change | n | Week 24 | Week 48 | Change |
| All subjects | 19 | 27 ± 17 | 30 ± 16 | 3 | 20 | 33 ± 20 | 40 ± 19 | 6 |
| Female | 12 | 32 ± 19 | 35 ± 18 | 3 | 14 | 34 ± 19 | 40 ± 20 | 6 |
| Male | 7 | 18 ± 7 | 21 ± 8 | 3 | 6 | 28 ± 23 | 38 ± 21 | 6 |

After receiving 24 weeks of galsulfase, subjects previously randomized to placebo experienced a 6 stair / minute increase in climbing rate. An increase in rate of stair climb is evident in both male and female subgroups, suggesting that the galsulfase treatment effect can be generalized to both genders. A small increase in climbing rate was also evident in subjects who continued to receive galsulfase weekly during study 03-06.

*Analysis by age categories*

For this analysis, the FDA reviewer divided the dataset into 3 subsets: those between the ages of 5 and 9 years of age, inclusive, named "Pre-pubertal", those between the ages of 10 and 14, inclusive named "Pubertal", and those between the ages of 15 to 29 years, named "Adult". Table 27 shows the rate of stair climbing by treatment groups, and by age categories, at baseline and at week 24 of Study 03-05.

**Table 27. Effect of age in the rate of stair climbing in Study 03-05**

| Age Categories | Galsulfase | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Week 24 | Change | n | Baseline | Week 24 | Change |
| Pre-Pubertal | 7 | 24 ± 16 | 31 ± 12 | 7 | 9 | 28 ± 19 | 31 ± 20 | 3 |
| Pubertal | 5 | 21 ± 12 | 28 ± 20 | 7 | 7 | 34 ± 20 | 36 ± 23 | 2 |
| Adult | 7 | 14 ± 9 | 22 ± 20 | 8 | 4 | 33 ± 16 | 29 ± 15 | 2 |

All age categories within the galsulfase-treated group had greater increases in rate of climbing in the 3-minute stair climb test, compared to their counterparts treated with placebo. There was no consistent trend between age and baseline rate of stair climbing.

*Analysis by severity of endurance impairment at baseline*

One way to analyze the 3-minute stair climb test is to divide the dataset into tertiles according to the degree of impairment in endurance, measured by the 12 MWT. The FDA reviewer used the same tertiles used in the analysis of the effect of galsulfase in the 12 MWT (please refer to Table 16). The table below shows a summary of the changes in the rate of stair climbing in the 3-minute stair climb test, according to the severity of endurance at baseline, measured by the 12 MWT.

**Table 28. Rate of stair climbing by baseline distance walked in studies 03-05 and 03-06**

| Distance walked (meters) | Galsulfase | | | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Wk 24 | Δ 24-B | Wk 48 | Δ 48-24 | n | Baseline | Wk 24 | Δ 24-B | Wk 48 | Δ 48-24 |
| 9.2 - 208 | 9 | 13 ± 10 | 22 ± 16 | 9 | 23 ± 14 | 1 | 4 | 11 ± 4 | 15 ± 8 | 4 | 17 ± 5 | 1 |
| 210 - 360 | 7 | 21 ± 8 | 28 ± 18 | 7 | 34 ± 18 | 6 | 6 | 26 ± 5 | 26 ± 11 | 0 | 34 ± 9 | 8 |
| 369 - 685 | 3 | 36 ± 14 | 40 ± 13 | 4 | 41 ± 6 | 1 | 10 | 41 ± 19 | 44 ± 21 | 4 | 51 ± 20 | 6 |

Δ 24 –B: change from baseline to Week 24; Δ 48-24: change from Week 24 to Week 48

This analysis, conducted among very small subsets of subjects with substantial variability, shows no trends related to an effect of galsulfase on the rate of stair climbing according to the distance walked at baseline.
Another analysis is to consider the tertiles at baseline for the outcome being measured in the test itself. The FDA reviewer divided the dataset into 3 tertiles of the rate of climbing, as follows:

**Table 29. Effect of impairment of climbing stairs at baseline in the rate of stair climbing during Studies 03-05 and 03-06**

| Stair Climb Rate (stairs / minute) | Galsulfase | | | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Wk 24 | Δ 24 -B | Wk 48 | Δ 48-24 | n | Baseline | Wk 24 | Δ 24-B | Wk 48 | Δ 48-24 |
| 2 – 15 | 9 | 9± 4 | 16 ± 8 | 7 | 19 ± 7 | 3 | 4 | 9 ±4 | 10 ± 4 | 1 | 13 ± 3 | 4 |
| 16 – 27 | 6 | 22 ± 4 | 25 ± 5 | 3 | 32 ± 13 | 6 | 7 | 22 ± 3 | 26 ± 10 | 4 | 32 ± 9 | 6 |
| 28 - 60 | 4 | 39 ± 6 | 54 ± 10 | 15 | 51 ± 11 | - 3 | 9 | 48 ± 11 | 50 ± 15 | 2 | 56 ± 13 | 6 |

Δ 24 –B: change from baseline to week 24; Δ 48-24: change from week 24 to week 48

The analysis does not reveal any clear trends in the effects of galsulfase on the rate of stair climbing according to the rate of climbing stairs at baseline. The only group that stands out was the least impaired subjects at baseline in the galsulfase group. This suggests that patients with less motion or pulmonary restriction have a more readily reversible component of the disorder. However, the subsets are very small, and the analysis is inconclusive.

*Effect of galsulfase on the 3-minute stair climb test in other studies in MPS VI*

Endurance, as measured by the 3-minute stair climb test, has been evaluated in Study 01-04. Briefly, open-label galsulfase was administered weekly to 10 subjects with MPS VI for 48 weeks, at the time that study report was written. Increases in the number of stairs climbed were seen in 9 of the 10 subjects at Week 6 (the first timepoint in which this outcome was assessed on treatment), and the mean percent increase at Week 48 compared to baseline was 148% (from a mean [± SD] of 50 ± 29.5 stairs at baseline to a mean of 111 ± 65 stairs at Week 48).

Though this study was conducted with the subjects' knowledge that they would be receiving active treatment, the fact that improvements in stair climbing were shown for the majority of subjects is to some extent supportive of the data obtained in the Phase 3, controlled study.

*Conclusion on the evidence of 3-minute stair climb test in support of the efficacy of galsulfase*

In summary, these data suggest that galsulfase contributes to increased endurance in subjects with MPS VI. However, the data suffer from the same baseline imbalance as the 12 MWT data, making interpretation difficult. Again, the increase in the rate of climbing in the placebo group, once treated with galsulfase for 24 weeks in the extension study, provide some evidence of efficacy. BioMarin comments that "although both tests measure endurance, the walk test is considered a measure not only of cardiovascular and pulmonary function, but also of mobility and quality of life. The Stair Climb Test correlates well with FVC and is considered a measure of

pulmonary function / capacity, although cardiovascular function, mobility, and quality of life also contribute to the results of this test."

It is unclear to what extent these 2 tests measure similar or different aspects of impairment in patients with MPS VI. If we believe that the 3-minute stair climb test correlates better with FVC (shown in studies of other conditions, but not shown with MPS VI), then this secondary endpoint would be distinct enough to provide independent support of the efficacy of galsulfase in this patient population. On the other hand, even if these 2 tests (12-minute walk test and 3-minute stair climb) are different tools for the evaluation of the same functions, the fact that they show beneficial changes in parallel, but not necessarily in the same subjects to the same extent, also provides additional support for the efficacy of galsulfase.

#### 6.1.4.6.1.6 Urinary GAGs

Baseline GAG excretion was similar in the two treatment groups: 346±128 and 330±114 μg/mg creatinine for subjects randomized to galsulfase and placebo, respectively. (As a point of reference, normal urinary GAGs excretion is 25 to 71 μg / mg creatinine for children aged 3 to 12 years and 7 to 38.5 μg / mg creatinine in children aged 13 to 18). No gender-related differences in urinary GAG excretion were apparent in the BioMarin survey data or in the literature references searched by this reviewer. Figure 10 is adapted from figure 14.2 – 1 "MPS VI Survey and Normal Subjects – Urinary GAG vs. Age" in the Clinical Study Report for the Survey Study 00-02. Among affected individuals, those over the age of 25 had the lowest urinary GAGs excretion, suggesting that their longevity may be related to less severe disease.

**Figure 10. Spread of Urinary GAGs levels according to age in healthy individuals and patients with MPS VI**


Table 30 below shows the reduction in urinary GAGs levels per treatment group over the 24 weeks of Study 03-05, and from Week 24 to Week 48 in Study 03-06

**Table 30. Changes in urinary GAGs over time in Studies 03-05 and 03-06, by treatment groups**

| Timepoint | Galsulfase | | | Placebo | | | Difference |
|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | Mean |
| Baseline | 19 | 346 | 128 | 20 | 330 | 114 | 17 |
| Week 1 | 18 | 329 | 131 | 19 | 367 | 134 | –38 |
| Week 4 | 19 | 116 | 48 | 20 | 348 | 126 | –232 |
| Week 6 | 19 | 103 | 45 | 19 | 339 | 95 | –237 |
| Week 8 | 19 | 94 | 47 | 19 | 354 | 107 | – 260 |
| Week 12 | 19 | 99 | 52 | 19 | 381 | 218 | –282 |
| Week 18 | 19 | 91 | 44 | 19 | 349 | 199 | –258 |
| Week 24 | 19 | 85 | 35 | 19 | 317 | 80 | –232 |
| Week 36 | 18 | 89 | 38 | 17 | 98 | 25 | –9 * |
| Week 48 | 18 | 96 | 35 | 17 | 97 | 30 | –1 * |

Urinary GAGs measured in μg / mg creatinine
* Both groups were treated with galsulfase 1 mg / kg weekly from Week 24 to Week 48

While the urinary GAGs remained constant in the placebo group during the 24 weeks of Study 03-05, it decreased by an average of 73 % from baseline in the galsulfase-treated group. Of note, most of the reduction occurred by Week 4. The analysis of variance adjusted for baseline was the primary method for data analysis. It showed an estimated mean ± SE difference at Week 24 between placebo and galsulfase of - 227 ± 18 μg / mg creatinine, with a 95 % confidence interval of -265 to -190 μg / mg creatinine ($p < 0.001$). Sensitivity analyses (excluding site as a covariate, a Student's t-test on the difference from baseline, and Wilcoxon test on the difference from baseline) yielded significant differences between groups.

A similar effect was observed in the placebo group at Weeks 36 and 48, after these subjects were switched to galsulfase.

Another analysis specified in the protocol was a responder analysis, with a responder defined as a subject with a ≥ 50 % reduction in urinary GAG excretion from baseline to Week 24. None of the placebo subjects were responders, whereas 17 of the 19 randomized to galsulfase were responders. The Fisher's exact test comparing the proportion of responders yielded a $p < 0.001$.

Effect of Galsulfase on urinary GAGs reduction by gender

Table 31 shows the mean reduction of urinary GAGs over the 24 weeks of Study 03-05 according to treatment group and gender:

**Table 31. Effect of gender on urinary GAGs in Study 03-05**

| Gender | Galsulfase | | | Placebo | | |
|---|---|---|---|---|---|---|
| | n | Change from Baseline | % Change from Baseline | n | Change from Baseline | % Change from Baseline |
| Female | 12 | -269 ± 133 | -73 ± 12 | 14 | -19 ± 95 | 1 ± 34 |
| Male | 7 | - 250 ± 68 | - 73 ± 15 | 5 | - 40 ± 54 | - 7± 16 |

As shown in the table the treatment effect did not appear to depend on gender.

*Tertiary endpoints*

The tertiary endpoints differed between Study 03-05 and its extension (Study 03-06). BioMarin altered the endpoints for the extension study (change in pulmonary and cardiovascular function), because they reasoned that a study could demonstrate evidence of efficacy only after more prolonged treatment with galsulfase. For a complete discussion of the appropriateness of endpoints please refer to Section 6.1.2 of this review.

Tertiary endpoints for the controlled part of the study (Study 03-05) included:

- Joint pain and stiffness and physical energy level

  These outcomes were measured using a 0 (no pain) to 10 (severe pain) visual analog scale, where pain or stiffness were recorded pre- and post activity (activity being the first of either the first 12-minute walk test or the first 3-minute stair climb for a particular visit). The pain scores were low overall at baseline and did not change much in either group by Week 24. Not all subjects reported pain; only 17 subjects with galsulfase and 19 subjects on placebo reported pain and were included in the analysis. Table 32 shows the scores in pre-activity and post-activity pain and the changes from baseline to Week 24:

**Table 32. Joint pain scores pre- and post-activity by treatment groups at baseline and Week 24 of Study 03-05**

| Group | Baseline | Week 24 |
|---|---|---|
| Galsulfase pre-activity (n=17) | 3.0 ± 3.6 | 1.2 ± 1.6 |
| Placebo pre-activity (n=19) | 2.2 ± 3.0 | 1.3 ± 2.3 |
| Difference in changes from baseline to week 24 | - 0.8 ± 1.1 | |
| p-value for change from baseline between groups | 0.49 | |
| Galsulfase post-activity (n = 17) | 3.5 ± 3.0 | 2.8 ± 3.1 |
| Placebo post-activity (n = 19) | 2.9 ± 3.0 | 1.5 ± 2.0 |
| Difference in changes from baseline to week 24 | 0.9 ± 1.4 | |
| p-value for change from baseline between groups | 0.34 | |

These changes were small, with large variation within the groups, so no conclusion can be drawn. In addition, the changes from pre- to post activity pain scores in each subject did not change over time during the study in either treatment group.

Joint stiffness was also reported on a visual analog scale from 0 (no stiffness) to 10 (worst stiffness). Joint stiffness was reported by 16 subjects randomized to galsulfase and by 16 subjects randomized to placebo. The mean (± SD) change in joint stiffness scores from baseline to Week 24 in the galsulfase group was – 3.1± 2.8 and for the placebo was – 2.6 ± 2.4 (p = 0.61).

Physical energy was measured on a visual analog scale also from 0 (no physical energy) to 10 (highest physical energy), by both the subject and his / her parent(s). Both groups had exhibited a small increase from baseline to Week 24. In 16 galsulfase-treated subjects, the self-assessed scores increased from a mean (± SD) 5.8 ± 1.8 at baseline to 7.6 ± 2.3 at Week 24, whereas the mean score for the 17 subjects in the placebo group increased from 5.8 ± 2.0 to 7.8 ± 2.3. There were no statistically significant differences between the groups in the longitudinal analyses conducted. Also, these scores, assessed by the subject or by the parent, are difficult to interpret in the context of MPS VI, because of the confounding effect of wide variability of the course of disease and its complications.

- Shoulder range of motion

  Shoulder range of motion was assessed by active and passive flexion, extension, and lateral rotation, measured with a goniometer, preferably by the same person at every visit. The primary analysis of this endpoint was the comparison between groups of the changes from baseline to Week 24 in the average of left and right shoulder active flexion, only among the subset of subjects whose baseline range of motion was less than 90 degrees. Ten subjects in each group qualified for the primary analysis. The data are shown in Table 33.

**Table 33. Average of right and left shoulder active flexion at baseline and at Week 24 of Study 03-05, by treatment group**

| Group | Baseline | Week 24 |
|---|---|---|
| Galsulfase (n=10) | 69 ± 15 | 79 ± 16 |
| Placebo (n=10) | 75 ± 11 | 92 ± 10 |
| Difference in changes from baseline to Week 24 (Mean ± SE) | 4 ± 5 | |
| p-value for change from baseline between groups (adjusted for baseline) | 0.62 | |

The differences between groups did not reach statistical significance. Both subsets of subjects showed a trend in increased active flexion over the 24 weeks of the study, by approximately 10 degrees. The change is difficult to interpret as a clinical benefit to subjects activities of daily living. For shoulder passive flexion, active and passive extension, and active and passive lateral rotation, both groups showed small improvements to Week 24, with no difference between them.

- Coin pick up test

  This outcome was assessed as a measure of sensation and dexterity (fine motor skills). Subjects were to use only one hand to pick up as many coins as possible from a table in 1 minute. There were 50 coins in the table for the test. For subjects able to pick up all 50 coins within 1 minute, the total time elapsed was to be recorded as well (Table 34).

**Table 34. Number of coins picked up at baseline and at Week 24 of Study 03-05, by treatment group**

| Group | Baseline | Week 24 |
|---|---|---|
| Galsulfase (n=19) | 25.8 ± 7.1 | 34.9 ± 10.1 |
| Placebo (n=20) | 25.2 ± 11.4 | 32.7 ± 12.3 |
| Difference in changes from baseline to Week 24 | 0.2 ± 3.0 | |
| p-value for change from baseline between groups | 0.87 | |

Both groups showed improvement, and the results were inconclusive. Improvements in the placebo group suggests a training effect or expectation bias.

In study 01-04, an uncontrolled study, a similar test was conducted to assess the time required to pick up 10 coins and place them into a cup. The time required for the task decreased from baseline to Week 48 in all 10 subjects, by a mean of 17 seconds. Given the apparent improvement in the placebo group of Study 03-05, the results are difficult to interpret. Moreover, it is unclear how these results relate to the subjects' activities of daily living.

Tertiary endpoints that were evaluated at baseline in Study 03-05 and for which the examination for efficacy was based on data from extension study (Study 03-06) included:

- Respiratory function

  This outcome was assessed by pulmonary function tests using spirometry. At the request of FDA, this outcome was assessed not only at baseline, where the sponsor's purpose was to assess the baseline severity of respiratory dysfunction, but also at Week 24. Based on lack of evidence of benefit from the initial 24 weeks of pulmonary function data in Studies 00-01 and 01-04, BioMarin considered it unlikely that a treatment effect could be demonstrated on this endpoint by Week 24 in Study 03-05. Although the protocol called for certain subjects with tracheostomy to have pulmonary function tests if they could tolerate temporary occlusion of the tracheostomy, only those subjects without tracheostomies were assessed. There were no changes in pulmonary function tests in either treatment group from baseline to Week 24 of Study 03-05 (Table 35)

**Table 35. FEV1 and FVC at baseline and at Week 24 in subjects without tracheostomy in Study 03-05**

| Respiratory Test | | Galsulfase | | | Placebo | |
|---|---|---|---|---|---|---|
| | n | Baseline | Week 24 | n | Baseline | Week 24 |
| FEV1 | 14 | 0.6 ± 0.4 | 0.6 ± 0.4 | 16 | 0.5 ± 0.1 | 0.5 ± 0.1 |
| FVC | 14 | 0.7 ± 0.4 | 0.7 ± 0.5 | 16 | 0.5 ± 0.2 | 0.5 ± 0.1 |

Table 36, adapted from BioMarin's application (Table 11-14), shows mean changes in respiratory parameters assessed with spirometry from baseline to Week 24.

**Table 36. Change from baseline to Week 24 in respiratory function outcomes measured in selected subjects in Study 03-05**

| Respiratory Test (unit) | n [1] | | Estimated Difference | 95% Confidence Interval | p-value [2] |
|---|---|---|---|---|---|
| | Galsulfase | Placebo | | | |
| FET (sec) [3] | 11 | 12 | 1.26 ± 0.734 | –0.29, 2.82 | 0.10 |
| FVC (L) [4] | 14 | 16 | 0.01 ± 0.045 | –0.09, 0.10 | 0.84 |
| $FEV_1$ (L) [5] | 14 | 16 | 0.03 ± 0.033 | –0.04, 0.09 | 0.44 |
| MVV (L/min) [6] | 12 | 15 | 3.02 ± 2.527 | –2.20, 8.38 | 0.24 |
| FIVC (L) [7] | 14 | 16 | 0.04 ± 0.045 | –0.05, 0.14 | 0.33 |
| FIR (L / sec) [8] | 11 | 12 | 0.23 ± 0.120 | –0.03, 0.48 | 0.078 |

[1] The number of patients in each treatment with both baseline and Week 24 measurements without a tracheostomy is displayed in the columns under 'n'.
[2] This is the p-value associated with treatment from an ANOVA model with treatment group, baseline measurement, and site as covariates. A positive value for the estimated difference indicates an improvement in the group receiving galsulfase
[3] Forced expiratory time
[4] Forced vital capacity
[5] Forced expiratory volume in one second
[6] Maximum ventilatory volume
[7] Forced inspiratory vital capacity
[8] (best) Forced inspiratory rate

These changes were marginal, and neither statistically nor clinically significant. BioMarin pointed out that the between-group differences in forced inspiratory rate and, to a lesser extent, in MVV and FET, suggest improvement in rib cage excursion due to improved strength or flexibility. The clinical significance of these changes is unknown and other parameters that measure related physiologic outcomes (ventilatory capacity) did not change by the same magnitude. BioMarin demonstrated a correlation (conducted as post-hoc analysis) between changes in MVV and changes in the 12-minute walked distance and the number of stairs climbed in the 3-minute stair climb test at Week 24 ( $r^2 = 0.23$ and $r^2 = 0.15$, respectively). The correlation between the changes in the 2 parameters is weak and any correlation would not be in itself supportive of a benefit in ventilatory capacity, when the between-group differences do not demonstrate a beneficial effect directly.

- Cardiac function and health resource utilization data were collected but were not included in this application.
- Visual examination was dropped from the efficacy endpoints listed because a sizable proportion of subjects had no visual acuity assessments at baseline and some of the centers did not follow protocol-specified methods of assessment of visual acuity.

### 6.1.5 Clinical Microbiology

The product reviewed in this application is not an antimicrobial, therefore this section is not applicable.

### 6.1.6 Efficacy Conclusions

MPS VI is a rare, complex disorder that results from a progressive accumulation of GAGs in multiple tissues and organs, at different rates for different individuals. The choice of the 12-minute walk test as the primary endpoint to provide evidence of efficacy was based on the potential capacity of this outcome to represent beneficial changes in diverse systems and organs affected by MSP VI, such as the locomotor, cardiovascular and respiratory systems. Prior to starting clinical studies with galsulfase, BioMarin or other investigators have explored its enzymatic activity in studies in fibroblasts and in a feline model of MPS VI.

Clinical development of galsulfase consisted of two small studies, one dose-controlled and one uncontrolled (Studies 00-01 and 01-04, respectively), and a Phase 3, randomized, placebo-controlled study of 24 weeks followed by an uncontrolled extension study (Studies 03-05 and 03-06). In addition, BioMarin conducted a cross-sectional survey of 121 patients with MPS VI to gather data on outcomes and disease characteristics of this rare population.

Study 00-01 was a dose-controlled, 24-week study of galsulfase in 7 subjects with MPS VI, 4 of these randomized to the lower dose, 0.2 mg / kg of galsulfase IV weekly, and 3 randomized to the higher dose, 1 mg / kg IV weekly. After the initial 24 weeks, the 5 remaining subjects have all been treated with the higher dose, 1 mg / kg / week, in an uncontrolled extension study.

BioMarin demonstrated an effect in the reduction of urinary GAGs that was substantial, ranging from 50 to 80 % at Week 24. The reduction of urinary GAGs persisted for at least 144 weeks of the controlled study and its uncontrolled extension. Although four of the 5 subjects that participated through Week 144 had improvements in the 6 MWT, the magnitude of these changes were highly variable, ranging from 40 to 231 % of baseline (92 to 236 meters) at Week 144, and one subject had no change from baseline. An effect of expectation bias cannot be excluded in the absence of a placebo control arm. The study was unable to demonstrate a uniform benefit in other clinical parameters. The reasons likely include the small sample size and the high variability of disease severity among the study participants.

Study 01-04 was an uncontrolled study of 10 subjects treated with galsulfase 1 mg / kg / week for 72 weeks. All subjects demonstrated improvements in the 12 MWT distances walked from baseline to Week 48, ranging from 50 to 600 meters (10 to 378 % of baseline at Week 48). An expectation bias cannot be excluded as an explanation for these results in an uncontrolled study. However, subjects in both Studies 00-01 and 01-04 were followed for one to 2 years and no significant deterioration of distances walked in the 6 MWT or the 12 MWT were observed.

The integrated analysis of efficacy is based mainly on Studies 03-05 and its open label uncontrolled extension Study 03-06. The primary endpoint was the 12 MWT. A beneficial change in this endpoint can provide evidence of improved endurance, a clinical outcome that is

important for this patient population. Thirty-nine subjects were randomized to receive galsulfase 1 mg / kg IV weekly or placebo for 24 weeks. After the controlled study, all 38 remaining subjects participated in an uncontrolled extension study in which all were treated with galsulfase.

The mean (± SD) difference in the between-groups changes from baseline to Week 24 in 12 MWT was 83 meters (± 45 meters), favoring the galsulfase group. The difference was statistically significant when tested with a repeated-measures longitudinal model weight-adjusted for a common baseline (p-value of 0.025 for an adjusted mean of 92 ± 40 meters). The difficulty in interpreting these data come from a substantial imbalance at baseline in the mean distances walked during the 12 MWT (227 ± 170 meters for the galsulfase group and 381 ± 202 meters for the placebo group). This review focused on analyses to address 2 possible phenomena that could affect interpretability of the efficacy data resulting from the imbalance observed at baseline: a differential regression to the mean in the galsulfase group and a ceiling effect at baseline for the placebo group.

The concern related to regression to the mean can be reduced by analyzing the rate of changes in distances that occurred in both groups prior to the baseline assessments in Study 03-05. An analysis of the rate of change from the distances walked from the Survey to the Screening in Study 03-05 and from Screening to Baseline in Study 03-05 failed to show shortening of distances between these timepoints that separated the galsulfase group from the placebo group.

The concern related to the ceiling effect in placebo subjects was attenuated by the demonstration of improvement in distances walked by the subjects originally randomized to placebo, after they were treated for 24 weeks with galsulfase in the extension Study 03-06.

While it is not appropriate to extrapolate findings from 24-week data to longer experiences with galsulfase treatment, it is appropriate to borrow some of the evidence from the open-label long-term studies 00-01 and 01-04 to establish that the clinical benefit observed in the controlled study is at least maintained in more prolonged exposure to treatment, with the possibility that some additional improvement may be achieved. This is corroborated by some additional benefit in endurance achieved by subjects who were treated for 48 weeks with galsulfase during both Study 03-05 and 03-06, as well as by subjects treated with galsulfase for 48 weeks in study 01-04 and longer in study 00-01.

Data obtained from stir climbing testing in Study 03-05 provide supportive evidence to a benefit in endurance. Whereas the between-groups rates of stair climbing were also substantially imbalanced at baseline, the combined stair-climbing data from Study 03-05 and 03-06 support the efficacy of galsulfase in increasing endurance for patients with MPS VI.

FDA views the substantial and persistent reductions in urinary GAGs with treatment not as a direct clinical benefit, but as a pharmacodynamic endpoint of enzyme activity.

# 7 INTEGRATED REVIEW OF SAFETY

## 7.1 Methods and Findings

The review of safety for this application is based on the clinical study reports, SAS transport files containing line listings of adverse events, and relevant pre-clinical information.

Whereas the review of galsulfase efficacy relied primarily on the placebo-controlled study (03-05), the review of safety relies on all 3 clinical studies. MPS VI is a systemic disease affecting multiple organ systems. Thus, there is a considerable background rate of adverse events in this patient population, and placebo-controlled studies provide the best source of safety data. However, largely because of the very low prevalence of the disease, the clinical development program included uncontrolled studies, as well as a safety extension study. These studies provide important information related to long-term drug exposure, and comprise an important part of this review.

The safety data were derived from 3 clinical studies: a Phase 1 / 2 dose comparison study (00-01), a Phase 2 open label study (01-04) and the Phase 3, placebo-controlled study (03-05). The safety database is comprised of all subjects who received any amount of study drug. No safety data are reported in this application related to the survey study or from the 2 siblings (ages 3 and 7/12 years and 2 months, respectively) in Australia that are being treated with open label galsulfase under an investigator-sponsored study.

In each study, the safety assessments included laboratory evaluations, vital signs, physical examinations, signs and symptoms of MPS VI, adverse events, anti-galsulfase antibody levels, concomitant medications, serum complement, electrocardiograms and echocardiograms.

Exposure to galsulfase

The 56 galsulfase-treated subjects in these 3 combined studies received weekly infusions for variable durations of time. The majority received a dose of 1 mg /kg / week for up to 144 weeks. The total galsulfase exposure is estimated at approximately 57 person-years for the 1 mg / kg dose and 3 persons-years for the 0.2 mg / kg dose. The average exposure to the 1 mg / kg dose was approximately 68 weeks per subject, and the average exposure to the 0.2 mg / kg was 50 weeks per subject. The average exposure to placebo was 24 weeks. Table 37 shows the overall exposure of subjects to galsulfase during the clinical studies, including exposure up to the 120-Day Safety Update.

**Table 37. Exposure to Galsulfase in Clinical Studies as of the Safety Update**

| Exposure | Patients Receiving Any Dose | Patients Receiving 1 mg/kg | Patients Receiving 0.2 mg / kg |
|---|---|---|---|
| Any | 55 | 53 | 4 |
| > 3 months | 54 | 53 | 3 |
| > 6 months | 54 | 53 | 2 |
| > 9 months | 53 | 53 | 2 |
| > 1 year | 34 | 34 | 2 |
| > 1.5 years | 15 | 15 | 0 |
| > 2 years | 5 | 3 | 0 |
| > 3 years | 3 | 3 | 0 |

In the dose finding, Phase 1 / 2 study 00-01, 1 subject received galsulfase at 0.2 mg / kg during study 00-01 but dropped out after Week 3, and another subject was randomized to the same dose and received galsulfase for 32 weeks before withdrawing from the study. Two other subjects received galsulfase at a dose of 0.2 mg / kg for 59 and 69 weeks respectively, before switching to 1 mg / kg, with data available in this application for 161 weeks (including the 120-day Safety Update). Three other subjects received 1 mg / kg galsulfase from the study start to 161 weeks.

In study 01-04, 10 subjects received weekly galsulfase doses of 1 mg / kg / week for 89 weeks (including the 120-day Safety Update data).

In Study 03-05, 19 subjects received weekly galsulfase doses of 1 mg / kg for 24 weeks. At the end of Study 03-05, these 19 subjects continued to receive galsulfase 1 mg / kg for 24 weeks in the extension study 03-06, which was conducted with an open label, uncontrolled design. Nineteen subjects that were randomized to placebo during the placebo-controlled Study 03-05, received galsulfase treatment for 24 weeks in the open label extension study 03-06, at the same dose of 1 mg / kg administered as an intravenous infusion on a weekly basis.

Across all studies within the galsulfase development program, compliance was excellent, with fewer than 1% of galsulfase infusions missed: in the 2 subjects in study 00-01 who were assigned to 0.2 mg doses and subsequently switched to 1 mg weekly doses, 3 of 288 infusions were missed; of the other 3 subjects in study 00-01, 4 infusions out of 432 possible infusions were missed. In the Phase 2 study 01-04, 2 infusions were missed out of a possible 720 infusions, and in the Phase 3 study 03-05, only one infusion (out of 456 possible) was missed.

Table 38 shows the overall incidence and frequency of adverse events, as reported by BioMarin:

**Table 38. Overall Incidence and Frequency of Adverse Events by dose or treatment group in the clinical studies of galsulfase**

| Incidence and Frequency of Adverse Events (Studies 00-01, 01-04, 03–05 and 03-06) | | | | |
|---|---|---|---|---|
| | No. of Subjects / No. of Events | | | |
| | **0.2 mg/kg (n = 2)** | **0.2/1 mg/kg (n = 2)** | **1 mg/kg (n = 32)** | **Placebo/ 1 mg / kg (n = 20)** |
| Any adverse event | 2 / 29 | 2 / 131 | 32 / 1707 | 20 / 625 |
| Deaths | 1 / 1 | 0 / 0 | 0 / 0 | 0 / 0 |
| Discontinuations due to adverse events | 0 / 0 | 0 / 0 | 0 / 0 | 0 / 0 |
| Serious adverse events | 1 / 3 | 2 / 7 | 10 / 24 | 6 / 19 |
| Severe adverse events | 1 / 2 | 2 / 2 | 17 / 26 | 6 / 24 |
| Study drug–related adverse events | 2 / 14 | 2 / 33 | 21 / 274 | 10 / 41 |
| Adverse events during infusion | 1 / 11 | 2 / 31 | 23 / 330 | 13 / 44 |
| IAR's (study drug-related adverse events during infusion) | 1 / 11 | 2 / 26 | 19/ 215 | 8 / 30 |

Of note, all subjects experienced at least one AE. There were no discontinuations due to AE's.

### 7.1.1 Deaths

One death was reported in the application. Subject 14-040, a 15 year old male participant in the Phase 1 /2 study 00-01, elected to withdraw from the study 3 weeks after enrollment. His past medical history was relevant for a seizure episode in —, 17 months before enrollment in the study. He also suffered from severe depression, and had suicidal ideation. The reported reason for withdrawal from the study was poor impulse control and danger to self and others. He had been randomized to the 0.2 mg / kg dose of galsulfase and had received 3 infusions prior to withdrawal. Ten months after withdrawal, he was diagnosed with a malignant brain glioma, and 14 months after withdrawal, he was diagnosed with carcinoma of the colon. He died of complications of the brain glioma approximately 20 months after his last drug infusion. This subject was determined to have a germline mutation of the MSH2 gene (a DNA mismatch repair gene) that was believed to be the underlying cause of both the glioma and the carcinoma of the colon. This reviewer searched the medical literature and the Online Mendelian Inheritance in Man database (maintained by Johns Hopkins University) for evidence of linkage between the ASB gene and the MSH2 gene, and found none. The MSH2 gene map locus is 2p22 – p21. It is unlikely that galsulfase contributed to the death of this subject.

### 7.1.2 Other Serious Adverse Events

A total of 56 serious adverse events occurred in 20 subjects in the 3 studies (Table 39 and Table 40): two subjects had SAE's only while treated with placebo in the controlled study 03-05; two other placebo-treated subjects subsequently developed SAE's only while being treated with galsulfase in the extension study 03-06; and two subjects had SAE's both on placebo in the controlled study 03-05 and on galsulfase treatment during the extension study 03-06. All other subjects that suffered SAE's were treated with galsulfase only. Three of these occurred during infusion:

- Subject 14-045 in the Phase 1 study had face, neck and axilla urticaria at Week 76, after having milder urticarial symptoms at Weeks 55 and 73, after being switched from the 0.2 mg / kg dose to the 1 mg / kg infusion. He continued to have mild, localized urticarial reactions in subsequent infusions, intermittently, until Week 144, for a total of 22 events. He was treated with slowing the rate of galsulfase infusion, supplemental antihistamines (starting at Week 85), and once with methylprednisolone 15.5 mg intravenously prior to Week 85 infusion;
- Subject 026-006 in the Phase 3 study had an episode of apnea during infusion of galsulfase at Week 18, lasting for 1 minute. The episode was considered by the investigator to be unrelated to the galsulfase infusion and possibly caused by the pre-treatment with anti-histamine in the setting of severe upper airway obstruction, related to MPS VI.
- Subject 018-005 in the Phase 3 extension study had episode of respiratory distress. She was a 9 year old female subject with history of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea who came for infusion at Week 46 (21 weeks on galsulfase treatment) with symptoms of upper respiratory infection and fever, who developed cyanosis,

emesis, tachypnea and tachycardia, and oxygen desaturations. She was admitted to intensive care unit.

Forty-three SAE's occurred while subjects were treated with galsulfase and 12 while on placebo. A simple comparison of numbers of SAE's between groups could be misleading in establishing links between galsulfase and the particular SAE's. While 20 subjects were infused with placebo for 24 weeks, 36 subjects were infused with galsulfase for periods longer than 1 year on average, providing more opportunities for SAE's to occur and be captured in the study reports. The most frequent of these study drug-unrelated SAE's was pneumonia, observed in 10 subjects (3 subjects on placebo and 7 subjects on galsulfase). No pattern of SAE's is observed in the galsulfase groups.

Other notable SAE's from those reported: 2 subjects with congestive heart failure (1 on placebo and 1 on galsulfase treatment), spinal cord compression (galsulfase), and 2 subjects with apnea (both on galsulfase). These SAE's are seen in patients with MPS VI with relatively high frequency.

**Table 39. SAE's observed in all clinical studies in both treatment groups**

| SAE | Number of subjects | Number of events | During Infusion |
|---|---|---|---|
| Pneumonia | 10 | 10 | None |
| Respiratory Distress / Hypoxia | 3 | 5 | 1 |
| Airway obstruction / Apnea | 4 | 7 | 1 |
| ENT / Asthma | 4 | 6 | 1 |
| Neurologic | 7 | 8 | None |
| Abdominal | 7 | 7 | None |
| Musculoskeletal | 3 | 3 | None |
| Other Infections | 3 | 3 | None |
| Urticaria / allergy | 1 | 1 | 1 |
| Other SAE's | 6 | 6 | None |

ENT / Asthma include: Eustachian Tube dysfunction, abscess in tracheostomy site, adenoviral URI;
Neurologic include: headache, increased intracranial pressure, seizures, compression of spinal cord, syncope, glioma;
Abdominal include: umbilical and inguinal hernias, pain, colon cancer, adhesive ileus;
Musculoskeletal include: carpal tunnel syndrome, chest wall and toe pain;
Other Infections include: Viral illness. sepsis, cellulites;
Other include: impaired venous access, congestive heart failure, severe bleeding, unstable INR, lesion in eye graft.

**Table 40. SAE's occurring only in galsulfase-treated subjects, with time in study**

| Subject | Week when SAE observed | SAE | Severity |
|---|---|---|---|
| 1-014-040 | 1 | Vasovagal syncope | Moderate |
| 1-014-040 | 3 | Brain glioma | Severe |
| 1-014-040 | 3 | Colon Cancer | Moderate |
| 1-014-041 | 32 | Bilateral Carpal Tunnel Syndrome | Severe |
| 1-014-041 | 32 | Bilateral Eustachian Tube Dysfunction | Moderate |
| 1-014-041 | 79 | Impaired venous access | Moderate |
| 1-014-041 | 79 | Umbilical hernia | Mild |
| 1-014-044 | 4 | Hypoxia | Moderate |
| 1-014-044 | 4 | Paratracheal skin hypertrophy | Moderate |
| 1-014-044 | 70 | Airway obstruction | Moderate |
| 1-014-044 | 91 | Spinal cord / brain stem compression | Severe |
| 1-014-044 | 91 | Respiratory distress | Severe |
| 1-014-044 | 92 | Abscess in tracheostomy site | Moderate |
| 1-014-044 | 101 | Apnea | Mild |
| 1-014-044 | 182 | Viral Upper Respiratory Infection | Moderate |
| 1-014-045 | 33 | Otitis media | Severe |
| 1-014-045 | 76 | Urticaria face, neck and axilla | Moderate |
| 1-014-045 | 90 | Chronic airway obstruction / bronchoscopy | Moderate |
| 2-014-201 | 81 | Arm cellulitis | Moderate |
| 2-014-202 | 47 | Pneumonia | Moderate |
| 2-014-203 | 121 | Pneumonia | Moderate |
| 2-023-300 | 0 | Sleep apnea | Mild |
| 2-023-300 | 1 | Pneumonia | Moderate |
| 2-023-300 | 1 | Unstable INR | Mild |
| 2-023-300 | 6 | Acute breathless episode | Moderate |
| 2-023-300 | 20 | Pneumonia | Severe |
| 2-023-300 | 100 | Chest pain | Moderate |
| 2-023-301 | 0 | Sleep apnea | Moderate |
| 2-023-303 | 9 | Asthma | Moderate |
| 2-023-303 | 34 | Toe pain | Moderate |
| 2-023-303 | 117 | Pneumonia | Moderate |
| 3-018-005 | 46 | Respiratory distress | Moderate |
| 3-021-003 | 41 | Raised intracranial pressure | Severe |
| 3-021-003 | 45 | Sepsis | Severe |
| 3-021-004 | 22 | Viral illness | Moderate |
| 3-024-001 | 28 | Worsening inguinal hernia | Severe |
| 3-024-001 | 43 | Headache post-injury | Moderate |
| 3-024-005 | 31 | Bleeding | Severe |
| 3-024-005 | 31 | Pneumonia | Severe |
| 3-025-001 | 23 | Lesion in corneal graft | Severe |
| 3-025-003 | 33 | Pneumonia | Severe |
| 3-025-003 | 33 | Heart failure | Severe |
| 3-026-006 | 18 | Apnea | Severe |

## 7.1.3 Dropouts and Other Significant Adverse Events

### 7.1.3.1 Overall profile of dropouts

Fifty-six subjects with MPS VI participated in the 4 clinical studies reviewed under this application. Of these, 3 subjects dropped out, all for reasons not related to adverse events.
In the Phase 1 / 2 study, subject 40 dropped out after 3 weeks in the study due to "poor impulse control with danger to patient and others". From the same site, subject 50 dropped out of the study after Week 32. The stated reason is "patient or parent / legal guardian withdrew consent". Both these subjects were randomized to the 0.2 mg / kg dose of galsulfase.
In study 03-05, the phase 3 study, one subject (subject 020-006) dropped out of the study after Week 5, due to "patient withdrew informed consent". This subject had been randomized to placebo. In all 3 cases, the subjects or families specifically denied early withdrawal due to adverse events.

### 7.1.3.2 Adverse events associated with dropouts

This is not applicable, since there were no dropouts associated with adverse events.

### 7.1.3.3 Other significant adverse events

A safety concern that is common to intravenous infusion of a variety of therapeutic proteins is the occurrence of infusion reactions. These adverse events are also prominent in the clinical development of galsulfase.

Severe adverse events during infusion (4 subjects):

Subject 023-302, in Study 01-04, had infusion associated reactions (IAR's) that were considered severe, as follows: urticarial rash at Weeks 35 (accompanied by vomiting, considered moderate), 36 (accompanied by hypotension, considered moderate) and 38. The same subject continued to have episodes of mild rash through Week 54;

Subject 023-304, in Study 01-04, had severe abdominal pain during infusion of galsulfase at Week 15.

Subject 20-007, in Study 03-05, had severe conjunctivitis, dyspnea and retrosternal pain during infusion at Week 6. The subject also had episodes of retrosternal pain (mild) at Week 9, and intermittently reported headache and conjunctivitis during infusions. This subject required slowing the infusion to 5 – 7 hours and prophylactic steroids starting at Week 7.

Subject 20-002, in study 03-05, with edema and exanthema of the neck, required slowing the infusion rate to 18 – 20 hours at Week 24, and prednisolone pre-infusion starting at Week 23.

Moderate adverse events during infusions:

In the 3 studies overall, 8 galsulfase-treated subjects in the 1 mg / kg dose, 1 galsulfase-treated subject in the 0.2 mg / kg dose and 4 placebo-treated subjects experienced moderate adverse events during infusions. Moderate abdominal pain and vomiting occurred in the 1 subject in the 1 mg / kg galsulfase dose, moderate pyrexia in 3 subjects in the 1 mg / kg dose cohort and in 2 subjects in the placebo group. Rigors occurred in only 2 subjects in the 1 mg / kg dose cohort, while moderate headache occurred in 2 placebo subjects during infusions. Bronchospasm, cough, dyspnea and urticaria of moderate intensity occurred only in the 1 mg / kg galsulfase cohort.

Sponsor-defined "anaphylactoid" reactions

BioMarin defined a subset of infusion associated reactions as "anaphylactoid" reactions if the following conditions were met:

- Recurred during multiple infusions
- Responded to interruption of the infusion or slowing of the rate of infusion
- Responded to the administration of additional anti-histamines (beyond the regular pre-infusion dose of diphenhydramine 0.5 – 1.25 mg / kg) or steroids.

It is relevant to note that this definition of "anaphylactoid" reactions departs from a more widely used definition. Anaphylactoid reactions are generally defined as symptoms and signs consistent with an anaphylactic reaction, but for which the mechanism is not related to IgE. Anaphylactic and anaphylactoid reactions both generally carry a sense of severity related to generalized allergic or cytokine-mediated life threatening events. Galsulfase is a recombinant form of the endogenous ASB. The native enzyme has been reported to inactivate the leukotrienes that constitute the slow reacting substances of anaphylaxis and one would expect that inflammatory and / or vasopermeable effects of these mediators of inflammation would decrease during or following infusion with galsulfase. The clinical experience differs from this theoretic assumption.

A complete list of the subjects with recurrent infusion reactions that were described by BioMarin as "anaphylactoid" reactions in this application is shown in Table 41.

BioMarin investigated and reported on the potential relationship between the concomitant medications, presence of concurrent illnesses, underlying manifestations of MPS VI, or missed infusions as factors precipitating or increasing the frequency of anaphylactoid reactions. No relationship has been observed between these factors and the anaphylactoid reactions.

**Table 41. Infusion reactions fulfilling BioMarin's definition of anaphylactoid reactions**

| Subject | Symptoms of Reaction | Timepoint Reaction Started | Timepoints Reaction Occurred | Treatment | | |
|---|---|---|---|---|---|---|
| | | | | Antihistamine Increased | Infusion Interrupted or Slowed | Steroids |
| 1–014–045[a] | Urticaria, rash | Wk 55 | Wks 73, 76, 78, 80–88, 91, 95, 102, 115, 120, 129, and 144 | Yes | Yes | Proph*: Wk 85<br>Post-infusion: Wk 85 |
| 2–014–201 | Chills, fever, urticaria | Wk 41 | Wks 43, 50, and 58 | Yes | Yes | During infusion: Wk 43 |
| 2–023–302 | Hypotension, urticaria, vomiting, rash | Wk 35 | Wks 36–47 and 49–54 | Yes | Yes (incomplete infusion at Wk 35) | Proph: Wk 36<br>During infusion: Wk 36 |
| 3–020–002 | Facial edema, urticaria, exanthema, dyspnea, conjunctivitis | Wk 21 | Wks 22, 23 and 24 | Yes | Yes (incomplete infusions at Wks 22 and 23) | Prophylaxis: Wks 23, 24<br>During infusion: Wks 21 to 24 |
| 3–020–007 | Conjunctivitis, dyspnea, retrosternal pain, headache, chills, malaise, joint pain | Wk 6 | Wks 7, 9, 15, 17, and 19 | Yes | Yes (incomplete infusion at Wk 6) | Proph: Wks 7–10 and 20–24<br>During infusion: Wks 6, 17, 19 |
| 3–024–003 | Abdominal pain, fever, bronchospasm | Wk 18 | Wks 19 and 23 | Yes | Yes | During infusion: Wk 23 |
| 3–024–005 | Fever, retrosternal pain, abdominal pain, rigors | Wk 12 | Wks 14 and 22 | No | Yes | No |
| 3–026–005 | Nausea, rigors | Wk 7 | Wks 8, 12, 13, 19–21, and 24 | No | Yes | No |

[a] First received infusion at 1 mg / kg dose at Week 59
*Proph: Prophylactic use

In the absence of markers of histamine release, there are no characteristics to help distinguish these reactions as anaphylactic or anaphylactoid. For practical reasons, the distinction is not very important, as the measures to prevent or treat them are the same. On the other hand, knowledge of the presence of rising anti-galsulfase IgE titers could not only indicate the type of reaction, but could also call for early institution of more aggressive prevention of anaphylaxis.

### 7.1.4 Other Search Strategies

This reviewer used different classifications of adverse events to look for patterns of safety signals emerging from the safety data in the 3 clinical studies. For example: all infections (upper

or lower respiratory, urinary, skin, vaginitis, etc) were combined. All allergic-type reactions (urticaria, bronchospasm, etc.) were lumped together. It is clear from these search strategies that rash, urticaria, rigors, dyspnea occurred during infusions more frequently in subjects treated with galsulfase than with placebo. No other patterns emerged from these safety analyses. Due to imbalance between the number of subjects on galsulfase (36) and on placebo (20), and the much more prolonged exposure to galsulfase (from 24 to 144 weeks) than placebo (from 5 to 24 weeks), the interpretation of comparative frequencies of adverse events would not be informative.

### 7.1.5 Common Adverse Events

#### 7.1.5.1 Eliciting adverse events data in the development program

BioMarin collected adverse events in all studies by use of case report forms, which were audited and clarified for inconsistencies and unclear notes. The subjects were seen at the investigator sites at least weekly (on average), when infusions of study drug were being performed. The collection of AE's has been continuous through the 3 clinical studies. The approach used for eliciting and collecting AE's was the same in all 3 studies. Adverse events that were not clearly stated were subjected to a query by the BioMarin auditor, for which the site had to provide additional clarification.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

BioMarin made use of the MedDRA dictionary to classify and code adverse events. The terms described by investigators were also collected and transferred to the safety datasets.
This reviewer encountered a problem in that the Case Report Forms contained one line for the investigator to list an adverse event, and only one line at the end of the Adverse events page for comments. This format of the CRF does not encourage further description of the adverse events, except for the serious or severe adverse events, and does not encourage listing the clinical diagnoses made in the majority of the adverse events investigated, as they were described in the case report forms (for example, rhinorrhea, fever, discolored mucus, headache were sometimes just listed as the individual symptoms, and not combined to make a diagnosis of sinusitis).

#### 7.1.5.3 Incidence of common adverse events

In the 4 studies, 2539 adverse events were reported (Table 42)

**Table 42. Common adverse events reported in all clinical studies**

| Common AE's | Galsulfase | Placebo | Total |
|---|---|---|---|
| During Infusion | 401 | 15 | 416 |
| Not during infusion | 1785 | 338 | 2123 |
| Total | 2186 | 353 | 2539 |

From the common adverse events manifested by the 36 subjects receiving galsulfase, the most common system organ class was Gastrointestinal disorders, affecting 33 of the 36 subjects (133

events). Thirteen of the 20 subjects receiving placebo had 58 AE's in that system organ class. The most common specific AE's within this class were vomiting, abdominal pain, diarrhea and nausea. The most common system organ class that contained adverse events among placebo-treated subjects was Infections and Infestations, that occurred in 19 of the 20 subjects, with 55 AE's. Upper respiratory infection (URI), nasopharyngitis, pneumonia, otitis media, and sinusitis were the most common specific AE's within this system organ class.

### 7.1.5.4 Common adverse event tables

Table 43 below contains a list of the specific adverse events, by decreasing order of frequency among galsulfase-treated subjects in all clinical studies, as compared to the incidence among placebo-treated subjects, irrespective of system organ class.

**Table 43.Incidence of AE's with frequency ≥ 14 % among galsulfase-treated subjects in Studies 00-01, 01-04 and 03-05**

| Specific AE | Galsulfase (n = 36) | | | Placebo (n = 20) | | |
|---|---|---|---|---|---|---|
| | N | % | Number of AE's | N | % | Number of AE's |
| Headache | 19 | 53 | 64 | 12 | 60 | 19 |
| Pyrexia | 18 | 50 | 61 | 8 | 40 | 21 |
| Arthralgia | 18 | 50 | 33 | 7 | 35 | 8 |
| Vomiting | 16 | 44 | 33 | 7 | 35 | 13 |
| URI | 15 | 42 | 41 | 7 | 35 | 9 |
| Abdominal pain | 14 | 39 | 20 | 6 | 30 | 13 |
| Diarrhea | 13 | 36 | 24 | 6 | 30 | 8 |
| Ear pain | 13 | 36 | 23 | 4 | 20 | 4 |
| Cough | 13 | 36 | 21 | 6 | 30 | 10 |
| Otitis media | 12 | 33 | 21 | 4 | 20 | 5 |
| Otorrhea | 10 | 28 | 29 | 0 | 0 | 0 |
| Chest Pain | 9 | 25 | 17 | 1 | 5 | 2 |
| Back Pain | 9 | 25 | 16 | 4 | 20 | 11 |
| Nausea | 9 | 25 | 16 | 5 | 25 | 8 |
| Rash | 9 | 25 | 30 | 2 | 10 | 3 |
| Pain in Extremity | 8 | 22 | 26 | 8 | 40 | 10 |
| Infusion Site Pain | 8 | 22 | 10 | 2 | 10 | 2 |
| Pruritus | 8 | 22 | 11 | 3 | 15 | 4 |
| Conjunctivitis | 7 | 19 | 13 | 0 | 0 | 0 |
| Pain | 7 | 19 | 11 | 1 | 5 | 1 |
| Nasal Congestion | 7 | 19 | 8 | 0 | 0 | 0 |
| Poor venous access | 7 | 19 | 7 | 3 | 15 | 3 |
| Ear infection | 6 | 17 | 16 | 2 | 10 | 2 |
| Pharyngitis | 6 | 17 | 11 | 1 | 5 | 1 |
| Myalgia | 6 | 17 | 23 | 1 | 5 | 1 |
| Urticaria | 6 | 17 | 25 | 0 | 0 | 0 |
| Pneumonia | 5 | 14 | 6 | 5 | 25 | 7 |
| Rhinorrhea | 5 | 14 | 11 | 4 | 20 | 6 |

From Table 43 above, it appears that Headache, Urticaria, Arthralgia, Otorrhea, Ear infection, Pharyngitis, Nasal Congestion, and Rash are more prevalent in galsulfase-treated subjects. However, a formal comparison between groups in the rates of these events is misleading, given the much longer duration of on-treatment follow up for 17 of the galsulfase-treated subjects. In addition, no pattern involving infection or allergic reaction is suggested by the data. Furthermore, the background prevalence and frequency of these symptoms and signs are so high in patients with MPS VI that no firm conclusion is possible.

This reviewer regrouped the adverse events that were not observed during infusion in Studies 00-01, 01-04 and 03-05, as follows:

**Table 44. Incidence of Adverse Events not associated with infusions (%) in descending order for the Galsulfase 1 mg / kg group using MedDRA terms, with at least 1 event reported for either Galsulfase group**

| Adverse Event | Placebo | Galsulfase | | Adverse Event | Placebo | Galsulfase | |
|---|---|---|---|---|---|---|---|
| | | 0.2 mg/kg | 1 mg/kg | | | 0.2 mg/kg | 1 mg/kg |
| n (%) | n=20 | n=4 | n=32 | n (%) | n=20 | n=4 | n=32 |
| Infection | 19 (95) | 3 (75) | 29 (91) | Wheezing, asthma, bronchospasm | 3 (15) | 0 (0) | 3 (9) |
| # Ear events | 11 (55) | 2 (50) | 22 (69) | Hypotension, vasovagal syncope | 1 (5) | 2 (50) | 2 (6) |
| Sinus events** | 17 (85) | 2 (50) | 18 (56) | Depression | 0 (0) | 1 (25) | 2 (6) |
| Arthralgia | 7 (35) | 2 (50) | 17 (53) | Dizziness | 2 (10) | 1 (25) | 2 (6) |
| Headache, migraine | 12 (60) | 2 (50) | 17 (53) | Insomnia | 0 (0) | 1 (25) | 2 (6) |
| Nausea and vomiting | 9 (45) | 2 (50) | 17 (53) | Urticaria | 0 (0) | 1 (25) | 2 (6) |
| Abdominal pain | 8 (40) | 2 (50) | 15 (47) | Anemia | 4 (20) | 0 (0) | 2 (6) |
| Fever | 8 (40) | 2 (50) | 14 (44) | Cardiac failure, cardiomegaly | 3 (15) | 0 (0) | 2 (6) |
| Viral infection, flu-like illness | 3 (15) | 3 (75) | 13 (41) | Conduction disorder | 0 (0) | 0 (0) | 2 (6) |
| Diarrhea | 6 (30) | 2 (50) | 11 (34) | Edema | 2 (10) | 0 (0) | 2 (6) |
| Cough | 6 (30) | 3 (75) | 10 (31) | Exanthema | 1 (5) | 0 (0) | 2 (6) |
| Eye events* | 3 (15) | 2 (50) | 10 (31) | Palpitation, tachycardia | 0 (0) | 0 (0) | 2 (6) |
| Rash, eczema | 2 (10) | 2 (50) | 10 (31) | Paresis | 2 (10) | 0 (0) | 2 (6) |
| Pain in extremity | 8 (40) | 1 (25) | 10 (31) | Paresthesias | 1 (5) | 0 (0) | 2 (6) |
| Back pain | 4 (20) | 1 (25) | 9 (28) | Restrictive pulmonary disease | 3 (15) | 0 (0) | 2 (6) |
| Bronchopneumonia/Pneumonia | 5 (25) | 0 (0) | 9 (28) | Spinal cord compression | 2 (10) | 0 (0) | 2 (6) |
| Pain, post-op pain | 2 (10) | 2 (50) | 8 (25) | Tachypnea / Respiratory distress | 1 (5) | 0 (0) | 2 (6) |
| & Pharyngolaryngeal events | 2 (10) | 1 (25) | 8 (25) | Tonsillar hypertrophy | 1 (5) | 0 (0) | 2 (6) |
| Chest pain | 1 (5) | 1 (25) | 7 (22) | Obstructive airways disorder | 1 (5) | 1 (25) | 1 (3) |
| Pruritus | 2 (10) | 1 (25) | 7 (22) | Splenomegaly | 3 (15) | 1 (25) | 1 (3) |
| Infusion site pain, erythema | 1 (5) | 0 (0) | 7 (22) | Abdominal distension | 2 (10) | 0 (0) | 1 (3) |
| Gastroenteritis | 0 (0) | 1 (25) | 6 (19) | Abscess oral | 0 (0) | 0 (0) | 1 (3) |
| Hearing impaired | 2 (10) | 1 (25) | 6 (19) | Acute tonsillitis | 0 (0) | 0 (0) | 1 (3) |
| Apnea | 2 (10) | 0 (0) | 6 (19) | Anasarca | 0 (0) | 0 (0) | 1 (3) |
| Bronchitis, tracheitis | 5 (25) | 2 (50) | 5 (16) | Cardiac valve disease | 3 (15) | 0 (0) | 1 (3) |
| Inguinal, umbilical hernia | 3 (15) | 1 (25) | 5 (16) | Corneal lesion | 0 (0) | 0 (0) | 1 (3) |
| Myalgia | 2 (10) | 1 (25) | 5 (16) | Decreased oxygen saturation | 1 (5) | 0 (0) | 1 (3) |
| Neck pain | 2 (10) | 0 (0) | 5 (16) | Dysuria / Bladder pain | 0 (0) | 0 (0) | 1 (3) |
| Fatigue, asthenia, lethargy, malaise | 4 (20) | 1 (25) | 4 (13) | Edema | 0 (0) | 0 (0) | 1 (3) |
| Agitation, anxiety | 1 (5) | 0 (0) | 4 (13) | Epilepsy, seizure | 2 (10) | 0 (0) | 1 (3) |
| Constipation | 1 (5) | 0 (0) | 4 (13) | Flatulence | 1 (5) | 0 (0) | 1 (3) |
| Visual acuity reduced | 2 (10) | 0 (0) | 4 (13) | Furuncle | 2 (10) | 0 (0) | 1 (3) |
| Areflexia | 0 (0) | 1 (25) | 3 (9) | Stye | 2 (10) | 0 (0) | 1 (3) |
| Bacterial infection | 4 (20) | 1 (25) | 3 (9) | Hypertension | 0 (0) | 0 (0) | 1 (3) |
| Alopecia | 3 (15) | 0 (0) | 3 (9) | Nail discoloration | 0 (0) | 0 (0) | 1 (3) |
| Corneal opacity | 0 (0) | 0 (0) | 3 (9) | Proteinuria | 0 (0) | 0 (0) | 1 (3) |
| Dyspnea | 2 (10) | 0 (0) | 3 (9) | Pulmonary Hypertension | 1 (5) | 0 (0) | 1 (3) |
| Eyelid edema | 1 (5) | 0 (0) | 3 (9) | Vertigo | 0 (0) | 0 (0) | 1 (3) |
| Tooth disorder, discoloration | 2 (10) | 0 (0) | 3 (9) | Lower respiratory tract infection | 1 (5) | 2 (50) | 0 (0) |
| Urinary incontinence | 0 (0) | 0 (0) | 3 (9) | Fungal skin infection | 2 (10) | 1 (25) | 0 (0) |
| Glaucoma/Intraocular pressure increased | 1 (5) | 0 (0) | 3 (9) | | | | |

*Eye events: eye irritation, eye pain, pruritus, dry eyes, conjunctivitis
**Sinus events: sinusitis, rhinitis, rhinorrhea, nasal congestion, cold, URI
[&] Pharyngolaryngeal events: Pharyngolaryngeal pain, pharyngitis, throat irritation
[#] Ear events: Red Tympanic membrane, otitis media, middle ear effusion, otorrhea, ear pain, ear infection, mastoiditis, ear wax

A similar grouping of adverse events occurring during infusions in Studies 00-01, 01-04 and 03-05 was done with the following resulting table:

| Adverse event | Placebo | Galsulfase (mg / kg) | |
|---|---|---|---|
| | | 0.2 | 1 |
| Fever | 2 | 1 | 8 |
| Epilepsy, seizure | 1 | 0 | 0 |
| Loss of consciousness | 0 | 0 | 1 |
| Headache, migraine | 2 | 0 | 5 |
| Paresthesias | 0 | 0 | 1 |
| Nausea and vomiting | 1 | 0 | 5 |
| Abdominal pain | 0 | 0 | 2 |
| Cardiac failure, cardiomegaly | 0 | 0 | 1 |
| Chest pain | 0 | 1 | 3 |
| Palpitation, tachycardia | 0 | 1 | 0 |
| Conduction disorder | 0 | 1 | 0 |
| HTN | 1 | 0 | 2 |
| Hypotension, vasovagal syncope | 0 | 1 | 1 |
| Wheezing, asthma, bronchospasm | 0 | 0 | 2 |
| Tachypnea / Respiratory distress | 0 | 1 | 1 |
| Oxygen saturation decreased | 1 | 0 | 2 |
| Obstructive airways disorder | 0 | 0 | 1 |
| Apnea | 0 | 0 | 1 |
| Cough | 0 | 0 | 1 |
| Dyspnea | 1 | 0 | 4 |
| Arthralgia | 0 | 0 | 1 |
| Pain in extremity | 1 | 0 | 1 |
| *Eye events | 0 | 1 | 2 |
| **Sinus events | 0 | 0 | 1 |
| &Pharyngolaryngeal events | 0 | 0 | 1 |
| Face, head and neck edema | 0 | 0 | 1 |
| Edema | 0 | 0 | 1 |
| Exanthema | 0 | 0 | 1 |
| Pruritus | 1 | 1 | 0 |
| Rash, eczema | 0 | 1 | 2 |
| Urticaria | 0 | 1 | 3 |
| Adjustment disorder | 0 | 0 | 1 |
| Agitation, anxiety | 0 | 0 | 1 |
| Confusional state | 0 | 0 | 1 |
| Fatigue, asthenia, lethargy, malaise | 0 | 0 | 3 |
| Pain, post-op pain | 0 | 0 | 2 |
| Rigors | 0 | 0 | 5 |

*Eye events: eye irritation, eye pain, pruritus, dry eyes, conjunctivitis
**Sinus events: sinusitis, rhinitis, rhinorrhea, nasal congestion, cold, URI
& Pharyngolaryngeal events: Pharyngolaryngeal pain, pharyngitis, throat irritation

From this table of adverse events that were observed during infusions, fever, rigors, headache, dyspnea and wheezing, nausea and vomiting, and rash and urticaria appear to be more frequent in galsulfase treated subjects. It is impossible to determine any dose response in these events,

given the much smaller exposure to the 0.2 mg / kg dose of galsulfase infused in 3- 4 subjects for 24 weeks, as compared to 31 subjects exposed to 1 mg / kg of galsulfase infusions over a period of 24 - 144 weeks.

The proposed labeling contains Table 45, which enumerates adverse events that were reported during the 6-month placebo-controlled Study 03-05 and occurred in at least 2 patients more in the galsulfase group than in the placebo group. The labeling notes that observed adverse events in the Phase 1, Phase 2, and open-label extension studies were not different in nature or severity.

**Table 45. Number and (%) of Patients with Selected Adverse Events in the Placebo-Controlled Study with ≥ subjects on galsulfase than on placebo**

| Adverse Event | Galsulfase (n = 19) | Placebo (n = 20) |
|---|---|---|
| | No. Patients (%) | No. Patients (%) |
| All | 19 (100) | 20 (100) |
| Abdominal Pain | 10 (53) | 6 (30) |
| Ear Pain | 8 (42) | 4 (20) |
| Pain | 5 (26) | 1 (5) |
| Conjunctivitis | 4 (21) | 0 |
| Dyspnea | 4 (21) | 2 (10) |
| Rigors | 4 (21) | 0 |
| Chest Pain | 3 (16) | 1 (5) |
| Pharyngitis | 3 (16) | 1 (5) |
| Areflexia | 2 (11) | 0 |
| Increased Corneal Opacification | 2 (11) | 0 |
| Face Edema | 2 (11) | 0 |
| Gastroenteritis | 2 (11) | 0 |
| Hypertension | 2 (11) | 0 |
| Malaise | 2 (11) | 0 |
| Nasal congestion | 2 (11) | 0 |
| Umbilical Hernia | 2 (11) | 0 |

7.1.5.5 Identifying common and drug-related adverse events

MPS VI is a disorder that affects multiple body systems in variable degrees of severity, and children and adolescents affected by the disease commonly manifest signs and symptoms that can be difficult to distinguish from a pattern of events related to a study drug. This problem is magnified by the small sample size, and the fact that there was limited placebo experience. No clear relationship exists between any non-infusion adverse event and the treatment with galsulfase. On the other hand, adverse events occurred more frequently during infusions of

galsulfase than infusions of placebo (74 events in 11 of 19 galsulfase-treated subjects versus 13 events in 8 of 20 subjects infused with placebo, in the controlled Study 03-05). When placebo-treated subjects were converted to galsulfase treatment in the extension study 03-06, these subjects had adverse events with a pattern and frequency similar to those subjects initially randomized to galsulfase in the controlled study 03-05. For infusion-associated reactions (AE's that were considered to be drug-related by the site investigator), the numbers are equally clear: 30 of the 56 galsulfase-treated subjects (this denominator includes those on placebo that were converted to galsulfase in study 03-06) had such adverse events. These AE's include rash, urticaria, pyrexia, rigors, hypotension, dyspnea, headache, retrosternal pain, nausea, edema (including angioneurotic edema), conjunctivitis, hypertension, exanthema, and abdominal pain. Of these AE's, it is important to note that rash, rigors, urticaria and hypotension were not seen in subjects infused with placebo. These AE's therefore can be confidently attributed to galsulfase, and they are not different in nature than those observed with infusions of other therapeutic proteins.

#### 7.1.5.6 Additional analyses and explorations

These adverse events that are clearly related to the infusion with galsulfase occurred similarly across age categories, genders and subjects with different titers of anti-galsulfase antibodies. The onset of these infusion-related reactions varied from Week 6 to as late as Week 55, except for a single case of hypertension that was associated with galsulfase infusion (infusion-associated reaction) at Week 1.

### 7.1.6 Less Common Adverse Events

The safety database presented in this application for galsulfase is 55 subjects exposed to galsulfase. The less common adverse events (for example, those seen in 1 subject once only) are not informative to predict infrequent adverse events in the MPS VI population after approval of this treatment and none of these were remarkable.

### 7.1.7 Laboratory Findings

#### 7.1.7.1 Overview of laboratory testing in the development program

Laboratory assessments of serum chemistries, complete blood counts, and urinalysis were collected at protocol-specified timepoints in each of the studies. The investigators were instructed to report clinically significant laboratory abnormalities (defined as those needed alterations in medical care) as adverse events, in addition to the reports under laboratory results. Other laboratory parameters, such as anti-galsulfase antibodies and components of complement were also measured at regular intervals, as well as during well defined adverse events, and were reviewed elsewhere (please refer to 7.1.10. Immunogenicity).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

All 3 clinical studies were reviewed for evaluation of the effects of galsulfase in the laboratory values. Where applicable, comments about drug versus placebo comparisons are made in the review; however, the comparisons are not very informative given the scarcity of laboratory abnormalities seen in the very small overall safety database presented in this application.

7.1.7.3 Standard analyses and explorations of laboratory data

*Analyses focused on measures of central tendency*

Anemia was the most common event reported, with a total of 4 episodes in 3 subjects out of 36 subjects treated with galsulfase, and 9 episodes reported for 8 subjects out of 19 treated with placebo. One subject on warfarin (subject 23-300) had 2 episodes of increased INR at weeks 2 and 3 of galsulfase treatment at 1 mg / kg during the Phase 3 study. There is no evidence to support an interaction between galsulfase and warfarin to prolong INR.

Table 46 shows some of the chemistry evaluations in galsulfase-treated and placebo-treated subjects in the 24 weeks of the Phase 3 study. Each measurement is shown in SI units as Mean ± SD.

**Table 46. Serum chemistry outcomes (mean +/- SD) in Study 03-05, by treatment group**

| Group | Week | n | Calcium (mmol/L) | Sodium (mmol/L) | Potassium (mmol/L) | BUN (mmol/L) | Glucose (mmol/L) | AST (U/L) | Alkaline Phosphatase (U/L) |
|---|---|---|---|---|---|---|---|---|---|
| Galsulfase | 0 | 19 | 2.4 ± 0.1 | 138.8 ± 3.3 | 4.1 ± 0.3 | 6.0 ± 2.5 | 5.0 ± 0.6 | 23.0 ± 7.4 | 219 ± 142 |
| | 24 | 19 | 2.4 ± 0.1 | 138.9 ± 2.0 | 4.1 ± 0.4 | 6.1 ± 2.8 | 4.8 ± 0.7 | 26.4 ± 8.3 | 261 ± 152 |
| Placebo | 0 | 20 | 2.4 ± 0.1 | 138.3 ± 2.0 | 4.1 ± 0.3 | 6.2 ± 3.6 | 4.7 ± 0.8 | 23.2 ± 6.3 | 206 ± 116 |
| | 24 | 19 | 2.4 ± 0.1 | 138.8 ± 2.6 | 4.1 ± 0.5 | 5.4 ± 2.3 | 5.3 ± 1.3 | 24.3 ± 11.9 | 206 ± 96 |

Except for a small increase in alkaline phosphatase in the galsulfase-treated group, no trends were noted in these or in other measures of central tendency for chemistry outcomes.

Table 47 is displayed for selected results of Hematologic parameters (Mean ± SD) evaluated during the Study 03-05, by treatment group.

**Table 47. Complete blood count outcomes (mean +/- SD) in Study 03-05, by treatment group**

| Group | Week | n | Hb (g/L) | WBC (X 10^9/L) | Basophils (%) | Eosinophils (%) | Platelets (X 10^9/L) |
|---|---|---|---|---|---|---|---|
| Galsulfase | 0 | 19 | 130 ± 12 | 5.6 ± 1.7 | 0.8 ± 0.7 | 0.4 ± 0.6 | 220 ± 52 |
| | 24 | 19 | 130 ± 11 | 5.8 ± 1.6 | 0.8 ± 1.0 | 1.4 ± 1.1 | 264 ± 61 |
| Placebo | 0 | 20 | 130 ± 11 | 6.4 ± 1.6 | 0.4 ± 0.5 | 0.3 ± 0.5 | 221 ± 39 |
| | 24 | 19 | 127 ± 13 | 5.9 ± 2.1 | 1.5 ± 1.3 | 0.3 ± 0.5 | 217 ± 50 |

No variations of any clinical significance were noted. There is a trend towards progressive increase in percent basophils among leukocytes in placebo-treated subjects. In some placebo-treated subjects the proportion of basophils reached 6.6 % of the leukocyte count. There is no clear explanation for this.

In the review of laronidase for the treatment of MPS I, there was a trend towards increased platelets among those receiving active treatment. The possible explanation for that phenomenon was the substantial reduction in size of the spleen in laronidase-treated subjects, with subsequent reduction of hypersplenism. In MPS VI, splenomegaly was not as prevalent as in MPS I, and although there is a trend towards some increase in platelet count among the galsulfase-treated subjects, as compared to placebo, it is not as evident as in the treatment of MPS I with laronidase.

*Analyses focused on outliers or shifts from normal to abnormal*

The only shift worthy of note is for alkaline phosphatase fluctuations: 1 of 29 galsulfase-treated subjects on 1 mg / kg shifted from lower than the lower limit of normal to higher than the upper limit of normal at Week 12 and 5 of 29 galsulfase-treated subjects on 1 mg / kg shifted from lower than the lower limit of normal to higher than the upper limit of normal at Week 24, while no placebo-treated subjects had a shift in this parameter. The actual values were not clinically significant, and no trends can be inferred. Furthermore there was no additional evidence of cholestasis, as the other liver enzyme suggestive of cholestasis, GGT, was normal, and no intrahepatic cholestasis was observed on liver imaging.

*Marked outliers and dropouts for laboratory abnormalities*

There were no marked outliers and there were no dropouts for laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

This reviewer correlated use of glucocorticosteroid medications with the incidence and titer of anti-galsulfase antibodies. Use of glucocorticosteroids was not associated with the rise of antibodies, and some of the largest titers of antibodies occurred in subjects being treated with these products either during infusions or between infusions.

Per protocol, the use of glucocorticosteroid medications was indicated in the prophylaxis of severe infusion reactions, so subjects such as 020-0002 and 020-007 have received repeated administration of prednisolone 21-hydrogen succinate prior to infusions of the double-blind agent.

Glucocorticosteroid steroids were used during infusion only in galsulfase-treated subjects, but these steroids were used in 11 galsulfase-treated subjects and in 6 placebo-treated subjects during non-infusions.

There is no apparent association between use of glucocorticoid steroids and suppression of anti-galsulfase IgG antibody formation.

#### 7.1.7.5 Special assessments

No other special assessments were conducted or analyses performed beyond these shown in the review.

### 7.1.8 Vital Signs

#### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs assessed in the clinical studies included systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. These vital signs were measured at screening, at baseline, just prior to the start of each infusion, immediately after completing each infusion, and 1 hour post-infusion. During each weekly infusion, vital signs were measured, at a minimum, every 30 minutes for the first hour, and every hour for the remainder of the infusion.
In addition, the subjects had weight and height assessed at regular intervals. Weight was measured at baseline and each week prior to infusion. Height (both sitting and standing) was measured at screening, at baseline, at Weeks 1, 6, 12, 36 and every 12 weeks through Week 144 in Study 00-01; at baseline and weeks 6, 12, 24, 48 and 72 in Study 01-04; and at screening, at baseline, and at weeks 1, 6, 12 and 24 for Study 03-05.

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The single placebo-control study in the clinical development of galsulfase was Study 03-05. This study enrolled 39 subjects and provides an opportunity for drug-control comparisons in vital signs. Overall, 1 placebo-treated subject and 2 galsulfase-treated subjects had blood pressure increased during infusions (these are listed as AE's) and 2 placebo-treated subjects and 2 galsulfase-treated subjects had pyrexia during infusions (also listed as AE's). No other clinically significant changes in vital signs were noted during the safety analysis from that study's data.

#### 7.1.8.3 Standard analyses and explorations of vital signs data

Fever, categorized under MedDRA preferred terms as pyrexia, hyperthermia, or increased body temperature, was a common change in vital signs that was reported as an AE. The incidence of fever was similar among the treatment groups in the controlled Study 03-05, with 8 subjects in each group experiencing about 40 episodes of fever during the study, during infusions or not. Subject 50 in study 00-01 had 11 episodes of hypotension, during infusion. These episodes were mild and did not require any medical intervention.

No exploratory analyses were conducted of the vital signs data

*Analyses focused on measures of central tendencies, analyses focused on outliers or shifts from normal to abnormal, and marked outliers and dropouts for vital sign abnormalities*

No analyses focused on measures of central tendencies were performed on vital signs. No analyses focused on outliers or shifts from normal to abnormal were done for vital signs. No marked abnormalities were observed in vital signs during the clinical studies and no neither study had dropouts due to abnormalities in vital signs

#### 7.1.8.4 Additional analyses and explorations

No additional analyses and explorations regarding vital signs were conducted.

### 7.1.9 Electrocardiograms (ECGs)

#### 7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG and echocardiograms were done in all subjects at screening, and Weeks 12, 24 and 48 in both studies 00-01 and 01-04, the baseline in Study 03-05, and at the baseline of the extension study 03-06. ECG and echocardiographic evaluations are important in this development because the disease MPS VI affects the heart structure and function with substantial morbidity. The reason for the monitoring therefore was to establish the baseline severity of heart structure and function and to investigate the effect of galsulfase on these parameters. It is not routine practice in the development of biologics to conduct studies of ECG changes similar to those necessary in the development of small molecules. Effects of biologic products in general on the QT interval are not reported, unless the biologic intent is to cause a specific effect on the heart conduction system.

#### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Progressive accumulation of GAG in the different heart structures contribute to the morbidity and mortality in MPS VI. Both ECG and echocardiogram testing, therefore, are important in the monitoring of progression of heart disease in these subjects. BioMarin proposed in the Phase 3 protocol to only investigate ECG and echocardiograms at baseline, with the purpose of providing an overall baseline cardiovascular impression for the subjects participating in their Phase 3 study. BioMarin did not expect that the 24 weeks of the controlled trial would be able to demonstrate any substantial change in the heart abnormalities present at baseline. BioMarin did provide with the 120-Day Safety Update some ECG and echocardiographic data for the subjects that originally participated in the controlled Study 03-05, and later continued in the open label, uncontrolled, extension Study 03-06. These procedures were performed at week 48 (24 weeks into Study 03-06).

#### 7.1.9.3 Standard analyses and explorations of ECG data

At baseline of Study 03-05, of the 39 subjects enrolled, 18 had no significant ECG findings, 9 in each group. Of the abnormal findings, there were 10 entries for sinus tachycardia (5 subjects in each group), as the most common reported ECG finding at baseline. Right axis deviation, with or without right ventricular hypertrophy, and left atrial enlargement accounted for some of the abnormal reports, and these were followed by intraventricular or atrio-ventricular delays or blocks.
Of the 18 subjects with no abnormal findings at baseline, only 9 had no abnormal findings at Week 48. Three of these subjects with ECG changes from baseline to Week 48 had changes considered significant by the investigators: subject 21-005 developed left atrial enlargement,

right axis deviation, and sinus tachycardia at week 48; subject 21-006 had right axis deviation, and subject 24-009 had developed first degree AV block and sinus tachycardia. Of the other 6 subjects, all developed sinus tachycardia. Some subjects experienced worsening of ECG findings from baseline to Week 48 (for example, subject 20-001 had right axis deviation and right atrial enlargement at baseline and developed clinically significant mitral stenosis and non specific ST and T wave abnormalities at Week 48). A few subjects had improvements in their ECG findings from baseline to Week 48.

Most subjects had abnormal echocardiographic findings at baseline and from these, most were considered clinically significant by the investigators. Ten subjects had pulmonary hypertension (6 were later randomized to galsulfase and 4 to placebo). Most of the clinically significant findings were thickened aortic and mitral valves, aortic and mitral stenosis, high mitral valve gradients and the pulmonary hypertension.

Of the 10 subjects with pulmonary hypertension at baseline, 5 had no evidence for this echocardiographic finding at Week 48 (3 placebo- and 2 galsulfase-treated subjects). On the other hand 2 placebo-treated subjects with no evidence of pulmonary hypertension at baseline had this finding at the Week 48 evaluation.

Given the prevalence of these abnormalities, and the variability of findings associated with ECG and echocardiographic findings, no conclusive interpretation of beneficial or deleterious effects of galsulfase on the heart is possible.

*Analyses focused on measures of central tendency, analyses focused on outliers or shifts from normal to abnormal, and marked outliers and dropouts for ECG abnormalities*

No analyses focused on measures of central tendency were conducted regarding ECG findings. No additional analyses focused on outliers or shifts from normal to abnormal were conducted. There were no marked outliers or dropouts related to ECG or echocardiographic findings.

#### 7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were performed.

### 7.1.10 Immunogenicity

#### 7.1.10.1 Anti-galsulfase antibodies

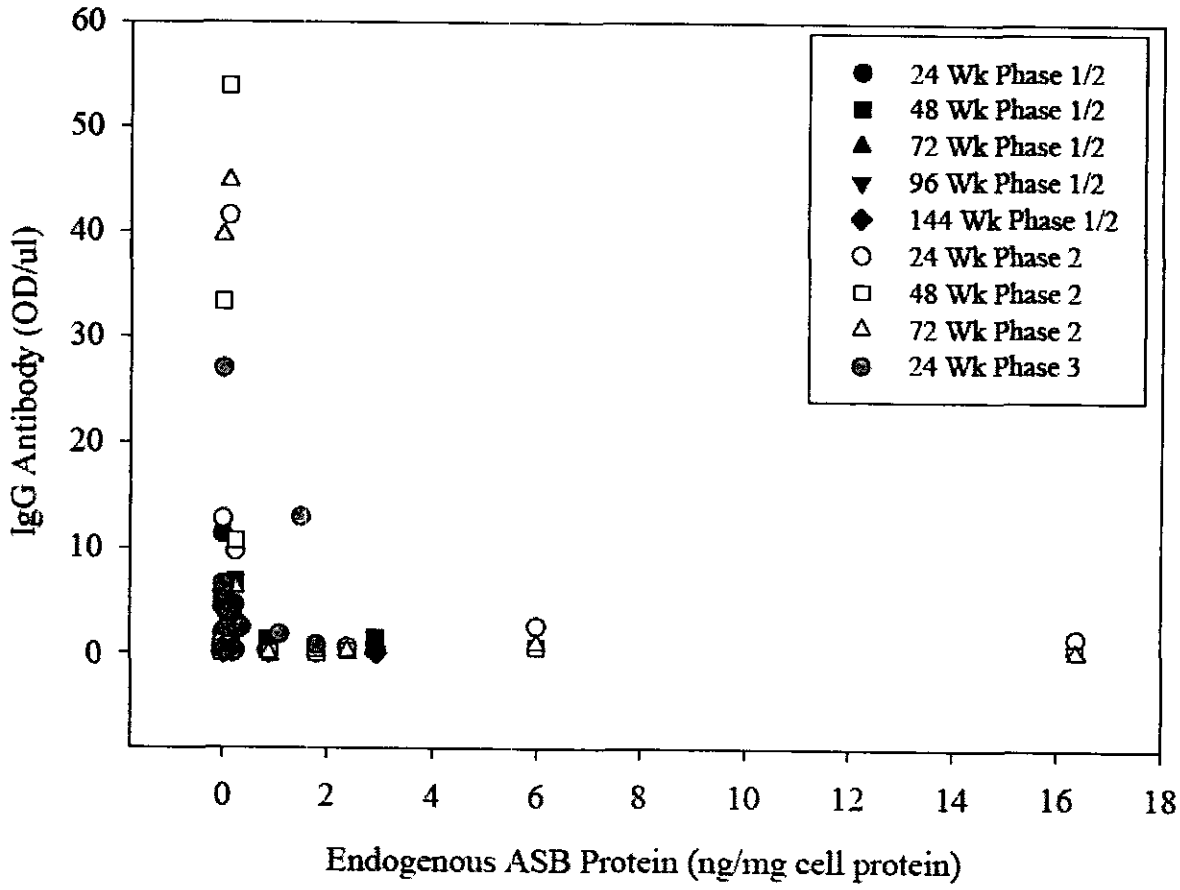
Anti-galsulfase IgG antibodies were assessed every 6 weeks in each of the studies. The lower limit of detection for anti-galsulfase antibodies with the assay employed was OD / µL. Of the 56 galsulfase-treated subjects in the 3 studies, only 1 subjects did not develop antibodies, and one subject (14-040) was not evaluated.

In general, antibodies were first detected in subjects between weeks 4 and 8 of the studies. In 29 of the 56 subjects treated with galsulfase the antibody levels never exceeded 2.0 OD / µL. BioMarin considered a threshold of 10 OD / µL a higher antibody titer, but without any rationale for the selected cutoff. Using this cutoff, and among galsulfase-treated subjects with at least 24 weeks of treatment, 1 of the 6 subjects in the Phase 1 / 2 study 00-01 had anti-galsulfase antibody titers greater than 10 (maximum of 11.4), 3 of 10 subjects in the Phase 2 study 01-04 had anti-galsulfase titers greater than 10 (maximum titer ranging from 11.2 to 54.4) and 7 of 38

subjects treated with galsulfase in the Phase 3 study 03-05 and 03-06 had antibody titers greater than 10 (peak antibody titers ranging from 13 to 64.9).

Data from the 3 studies analyzed together indicate an inverse correlation between the titers of anti-galsulfase antibody and concentration of endogenous ASB protein, as shown in Figure 11, provided by BioMarin.

**Figure 11. Anti-galsulfase antibody titers and endogenous ASB concentrations in all studies**




BioMarin provided, at the request of this reviewer, data on the endogenous ASB enzyme activity for subjects that participated in the Phase 3 study 03-05. The data shows discrepancies between ASB protein concentrations and enzyme activities in a few subjects, such that these subjects had no detectable protein concentration but had detectable enzyme activity in the assay used. No relationship can be established between the endogenous ASB enzyme activity and the titers of anti-galsulfase antibodies, but this conclusion is limited by the inconsistencies between the ASB protein concentration and activity assays.

The titers of anti-galsulfase antibodies increased over time from Week 4 to Week 48, then gradually decreased for the duration of the studies (72 weeks for study 01-04 and 144 weeks for study 00-01. Table 48 shows the variation of anti-galsulfase antibodies over time for each dose of galsulfase.

**Table 48. Variation of anti-galsulfase antibodies in the 3 studies (in OD / μL)**

| Timepoint (n) | Galsulfase 0.2 mg / kg | | Timepoint (n) | Galsulfase 1 mg / kg | |
|---|---|---|---|---|---|
| | Mean ± SD | Range | | Mean ± SD | Range |
| Baseline (4) | 0 ± 0 | 0 | Baseline (31) | 0.1 ± 0.1 | 0 – 0.2 |
| Week 6 (4) | 0.1 ± 0.1 | 0 – 0.2 | Week 6 (32) | 4.2 ± 9.2 | 0 - 48 |
| Week 12 (3) | 1.7 ± 2.9 | 0 – 5.1 | Week 12 (32) | 3.9 ± 5.7 | 0 - 27 |
| Week 24 (3) | 4.4 ± 6.1 | 0 – 11.4 | Week 24 (32) | 8.2 ± 13.9 | 0 – 64.9 |
| Week 48 (2) | 3.0 ± 2.8 | 1 – 4.9 | Week 48 (13) | 8.4 ± 16.5 | 0 – 53.8 |
| Week 72 (0) | N / A | N / A | Week 72 (13) | 6.4 ± 14.7 | 0 – 44.8 |
| Week 96 (0) | N / A | N / A | Week 96 (5) | 0.6 ± 0.6 | 0 – 1.6 |
| Week 144 (0) | N / A | N / A | Week 144 (4) | 1.1 ± 1.6 | 0 – 3.5 |

BioMarin has interpreted this decline in titers over time as suggesting development of tolerance. Importantly, a similar pattern of antibody rise and fall over time has been observed within studies using laronidase for the treatment of MPS I.

The level of antibody, time to first antibody development, and time of maximum antibody level was correlated with patient age (5-12 years, 13-18 years, ≥ 19 years), and gender. Younger patients developed antibodies sooner and had a higher maximum level than older patients. There were no differences in time to maximum antibody level among the age categories. There were no statistically significant differences between males and females for these 3 variables.

7.1.10.2 Effect of anti-galsulfase antibodies on the pharmacokinetic parameters

At least in one subject in Study 00-01, subject 014-041, serum ASB levels were below the limit of quantitation at weeks 12 and 24, timepoints in which the antibody titers were highest (5.1 and 11.4 OD / μL). By week 83, the subject's antibody titers were much lower (0.8 OD / μL) and the ASB serum levels were consistent with those in the group. In studies 01-04 and 03-05 pharmacokinetic parameters were affected by antibody titers above 10 OD / μL, with similar interference with ASB assay, but not in all subjects with the high titers. For 3 subjects in Study 03-05 with antibody titers over 10 OD / μL, both clearance and volume of distribution increased with the increase in titers.

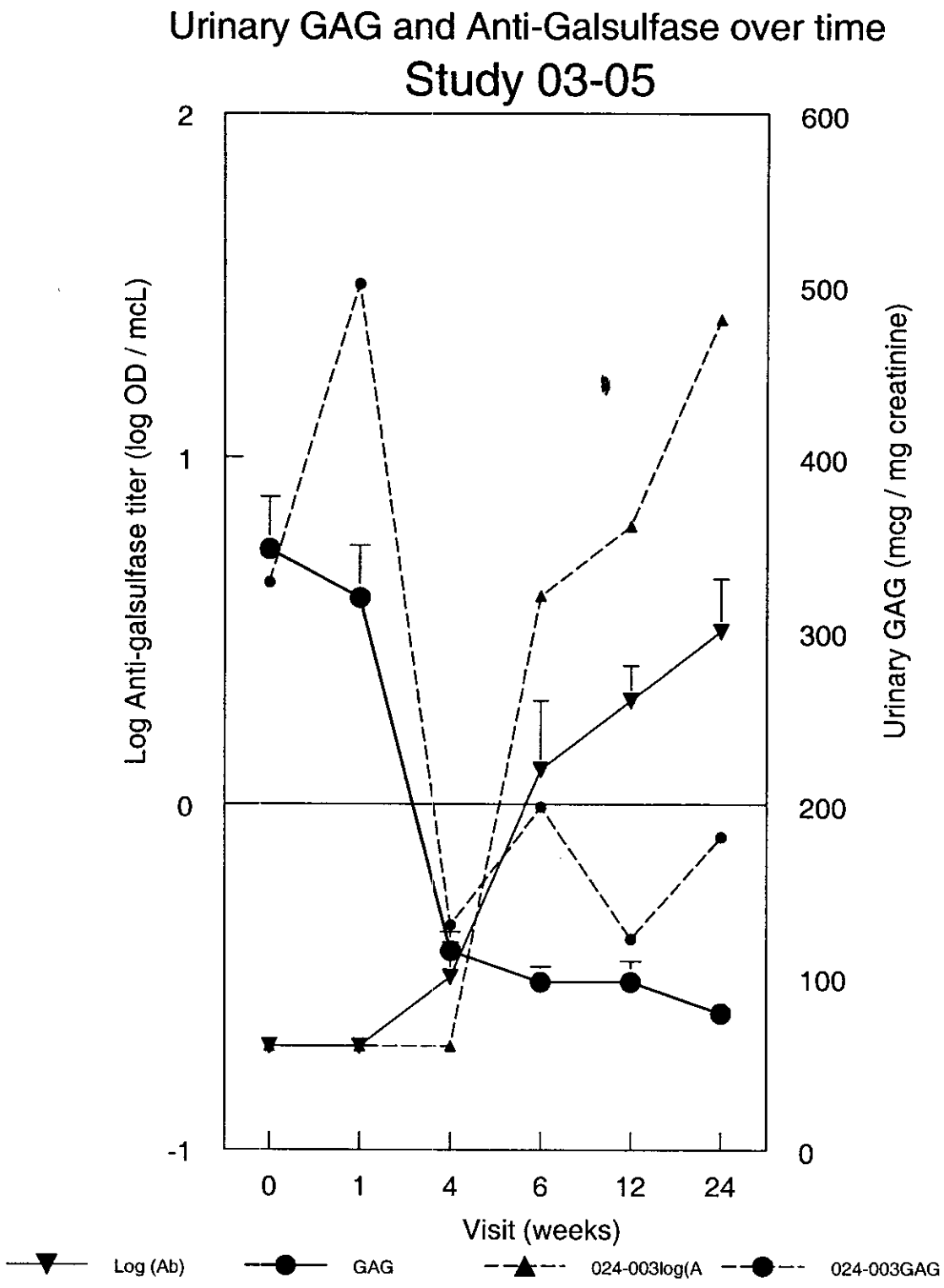
7.1.10.3 Effect of antibodies on urinary GAGs

This is an important analysis to determine if anti-galsulfase antibodies affect the lysosomal uptake of galsulfase and can potentially neutralize its effect on target organs and tissues. For all subjects, except subject 024-003 in the Study 03-05, the appearance or the peak of anti-galsulfase antibody titers did not correlate with the degree of reduction in urinary GAGs from baseline to that specific timepoint. Three of the subjects in study 03-05 had anti-galsulfase antibody titers greater than 10 OD / μL, and had clearance and distribution parameters increased. Two of them (024-005 and 026-002) had reductions in urinary GAGs that were in the same magnitude as the subjects with lesser antibody formation. The third was subject 024-003, who had a lesser reduction in urinary GAGs (45 % decrease at week 24) compared to other subjects in the galsulfase group (75% decrease at week 24) while anti-galsulfase antibody titers peaked at 27 OD / μL at week 24 (Figure 12). Subject 024-003 had evidence that the anti-galsulfase antibodies were neutralizing based on an *in vitro* assay demonstrating inhibition of ASB activity in the presence of the subject's serum.

BioMarin proposed that the lesser reduction in urinary GAGs was evidence of *in vivo* neutralization of galsulfase activity. This reviewer disagrees with BioMarin's view that these data suggest *in vivo* neutralization. Subject 024-003 urinary GAGs rose from 328 to 501 μg / mg creatinine between baseline and Week 1. Such fluctuations in urinary GAGs have occurred in untreated patients. If we consider the true baseline urinary GAGs level at 501, then a reduction to urinary GAGs in the range of 122 to 180 represents a reduction of urinary GAGs levels to the same magnitude as other subjects (Figure 12). This indicates that there is no evidence of *in vivo* antibody neutralization of the galsulfase effect, at least as reflected in urinary GAGs.

Maintenance of urinary GAGs reduction was observed in all subjects through the duration of the 3 clinical studies.

**Figure 12. Anti-galsulfase antibody titers and urinary GAGs**



7.1.10.4 Effect of glucocorticoid use on complement activation and anti-galsulfase antibody formation

No effect of use of glucocorticoid steroids, systemic or local, was observed on the titers of anti-galsulfase antibodies or on complement activation during infusion with galsulfase. No differences in urinary GAGs were noted in subjects while taking glucocorticoid steroids, as compared to the degree of urinary GAGs reduction in those subjects when not being given these medications.

7.1.10.5 Effect of anti-galsulfase antibodies on parameters of endurance and safety in the Phase 3 study

Table 49, adapted from BioMarin's application Table 14-110, shows the antibody titers at week 24 compared to number of AE's at week 24 and AE's cumulative from baseline to that timepoint, as well as to parameters of endurance and urinary GAGs

**Table 49. Anti-galsulfase antibody titers in ascending order, number of AE's and parameters of endurance in Study 03-05**

| Subject | Antibody | # AEs at Week 24 | | # AEs cumulative | | 12-minute walk | | Stair climb | | GAGs | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Overall | During infusion | Overall | During infusion | Baseline | Change from Baseline | Baseline | Change from Baseline | Baseline | Change from Baseline |
| 020-003 | 0.2 | 0 | 0 | 13 | 1 | 356 | 441 | 95 | 101 | 75 | -52 |
| 024-002 | 0.2 | 14 | 2 | 53 | 7 | 508 | -48 | 60 | 19 | 267 | -223 |
| 025-004 | 0.8 | 2 | 0 | 17 | 0 | 208 | 433 | 115 | 60 | 68 | -25 |
| 020-002 | 1.8 | 8 | 8 | 22 | 13 | 9 | -4 | 18 | 0 | 309 | -240 |
| 018-004 | 2 | 0 | 0 | 6 | 0 | 153 | 12 | 53 | 16 | 319 | -283 |
| 026-006 | 2.3 | 0 | 0 | 8 | 2 | 90 | -31 | 23 | 0 | 445 | -352 |
| 021-006 | 2.4 | 6 | 0 | 32 | 0 | 211 | 272 | 77 | -14 | 266 | -196 |
| 026-003 | 2.4 | 1 | 0 | 6 | 1 | 173 | 115 | 34 | 41 | 436 | -340 |
| 025-001 | 3.9 | 1 | 0 | 9 | 0 | 107 | 17 | 33 | 18 | 309 | -196 |
| 018-002 | 4.4 | 0 | 0 | 8 | 0 | 23 | 48 | 13 | 14 | 384 | -301 |
| 021-004 | 5.3 | 11 | 1 | 40 | 3 | 242 | 183 | 79 | 21 | 322 | -231 |
| 026-005 | 5.8 | 1 | 1 | 11 | 10 | 210 | 106 | 36 | 9 | 378 | -271 |
| 021-001 | 6.4 | 1 | 0 | 30 | 3 | 38 | 332 | 7 | 80 | 541 | -433 |
| 024-007 | 6.6 | 3 | 0 | 22 | 0 | 623 | 12 | 130 | 8 | 382 | -303 |
| 020-005 | 13 | 1 | 0 | 10 | 0 | 38 | 7 | 50 | 10 | 329 | -246 |
| 024-005 | 17.1 | 7 | 3 | 22 | 10 | 457 | 62 | 130 | -8 | 582 | -469 |
| 020-007 | 19.2 | 2 | 0 | 30 | 18 | 330 | 135 | 79 | 7 | 392 | -315 |
| 024-003 | 27 | 8 | 3 | 25 | 6 | 270 | 30 | 44 | 16 | 328 | -148 |
| 026-002 | 64.9 | 1 | 0 | 5 | 0 | 262 | -45 | 30 | 12 | 452 | -348 |

Antibody titers are measured as OD/ µL, AEs are measured as counts of events, 12 minute walk is measured in meters, stair climb is measured in number of stairs climbed in 3 minutes, and urinary GAG's are measured in µg / mg creatinine.

Since the antibody titers assessed during the 24 weeks of study 03-05 were generally at their peak at week 24, the intent of this table is to demonstrate a lack of correlation between antibody titers and frequency of AE's, as well as the lack of impact of these titers on parameters of endurance and urinary GAGs. In this sample of 19 subjects, no such correlation can be observed.

7.1.10.6 Complement activation

Complement parameters were assessed pre-and post-infusion at regular intervals in all 3 studies. Many of the subjects had sporadic, small, decreases in single complement parameters (either C3, C4 or CH%) during the study. In approximately 50 % of subjects with decreases in more than 1 parameter, anti-galsulfase titers rose to above 10 OD / μL, but the complement decrease did not occur in a timeframe consistent with the antibody rise. There was no correlation between decreases in complement and anaphylactoid reactions.

Subjects with complement decrease with additional descriptions:

- Subject 14-041, in Study 00-01, had CH50 titers decreased from 150 to 90 CAE post-infusion at Week 4, but without concomitant decreases in C3 and C4, and without any evidence of AE's.
- Subject 014-204 in the Phase 2 Study 01-04 had moderate decreases in all 3 components of complement after galsulfase infusions on Weeks 6, 12, 25 and 48. This subject had no infusion reaction, adverse events not during infusions that could be related to complement consumption, or laboratory abnormalities other than the complement components decrease.
- Subject 23-303 in the Phase 2 Study 01-04, an 8 year old girl, had evidence of complement activation with infusion, observed through reduction in C3, C4 and CH50, on Weeks 14, 18 and 24 of the study. Subsequently the subject did not have evidence of complement consumption until the end of the study. Her anti-galsulfase antibody levels became detectable at Week 4 (1.3 OD / μL), increased to 12 – 15 OD / μL between Weeks 6 and 24, then increased again to 34.1 – 43.5 OD / μL and remained elevated until Week 72. There were no infusion reactions associated with the complement consumption or evidence of other SAE's connected with the laboratory finding. This subject's microscopic urine findings revealed no blood cells but presence of protein, reported as 0.3, at Weeks 30 and 54. The subject had a toe amputation at week 36, but the case report form notes that she had a pre-existing toe deformity and the amputation was related to that fact, not to any complement-induced vasculopathy.
- Subjects 26-002 and 26-005, in the Phase 3 Study 03-05, had the 3 components of complement decreased in Weeks 12, 18 and 24, also without AE's during or after infusions or any laboratory alterations.

Four placebo subjects in the Phase 3 Study 03-05 also had decreases in 2 complement components post-infusion between Weeks 6 and 24, intermittently.

In conclusion, although sporadic decreases in components of complement were observed during galsulfase infusions, there is no evidence to suggest that complement consumptions was associated with infusion reactions or other AE's.

7.1.10.7 Effect of antibodies on infusion reactions or anaphylactoid reactions

Data from the 3 studies do not support a correlation between infusion reactions and, in particular, anaphylactoid reactions, with the titers of antibodies measured in the subjects treated with galsulfase in any of the 3 studies. The timing of elevation of anti-galsulfase antibody titers does

not correspond to the onset of anaphylactoid reactions. One possible exception is subject 020-007, in whom the antibody titers fluctuated from 10.5 at week 6 to 4.4 at Week 12 and then increased to 19.2 at Week 24. The subject was having anaphylactoid reactions through this period, but the antibody titers might have been decreased with use of prophylactic steroids starting at Week 7.

### 7.1.11 Human Carcinogenicity

There were no pre-clinical assessments for potential for carcinogenicity in the development of galsulfase. The treatment is intended as replacement for the deficient ASB activity and there is no rationale to suggest an increase risk for cancer in this patient population. Therefore, these assessments would not be applicable to the treatment and the condition being studied.

One subject developed both glioma and colorectal carcinoma 10 and 14 months after withdrawal from the study (after 3 doses of galsulfase only), but the pathogenesis of these neoplastic conditions appeared to be related to a pre-existing germline mutation in the MSH2 gene.

### 7.1.12 Special Safety Studies

There were no special safety studies conducted in the galsulfase clinical development program. The concerns related to the pharmacological class (generally speaking, infusion of therapeutic proteins being associated with infusion reactions) has been addressed in pre-clinical studies and early clinical studies with the generalized use of anti-histamine pre-treatment and slow infusion rates.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

This product does not have evidence of abuse potential or withdrawal symptoms.

### 7.1.14 Human Reproduction and Pregnancy Data

The application contains no data on human reproduction and pregnancy.

### 7.1.15 Assessment of Effect on Growth

Most patients with MPS VI are very short for their age. The mean height (± SD) for 120 subjects that participated in the MPS VI Survey study was 115 (± 26) cm and the mean weight was 30.5 (± 18) kg, for subjects with ages ranging from 4 to 56 years, most being between 4 and 18 years. In the Phase 3 Study 03-05 the mean (± SD) height for galsulfase treated subjects was 104 (± 13) cm, while it was 100 (± 13) cm for the placebo group. The mean weight for the galsulfase group was 24.6 (± 9) kg compared to 20.8 (± 8) kg for the placebo group.

Subjects in the placebo group had changes in height ranging from –1.5 cm to + 1.5 cm. Six subjects, all of whom were younger than 12 years of age, had increases in height > 1.0 cm in the 24-week study. Subjects in the galsulfase group had changes in height ranging from –2.0 cm to 3.6 cm. Nine patients in the galsulfase group had increases in height > 1.0 cm; 5 of these patients were older and 4 were younger than 12 years. There was no apparent relationship between age and increases in height. These data cannot lead to any conclusions regarding beneficial or detrimental effects of galsulfase on growth.

#### 7.1.16 Overdose Experience

No experience with overdose is reported in this application.

#### 7.1.17 Postmarketing Experience

As galsulfase is not licensed or approved in any country, there is no postmarketing experience with galsulfase.

### 7.2 Adequacy of Patient Exposure and Safety Assessments

The patient exposure to galsulfase was adequate for this very rare disease. The number of patients studied, although very small if compared to the majority of therapeutic products approved, was substantial for the prevalence of the condition. Longer controlled studies would have been desirable for the assessment of both efficacy and safety, but the BioMarin application contains sufficient safety information to guide physicians with a clear label. Additional, long term safety data will come from post-marketing studies and pharmacovigilance. The majority of AE's that can be reasonably attributed to galsulfase are infusion reactions, and these were studied and reported adequately in the CRF's for the subjects studied. Immunogenicity is another area of general concern when reviewing therapeutic biologic products. Anti-galsulfase antibody titers were monitored through the clinical studies, and galsulfase was determined to be highly immunogenic in these subjects. We cannot find evidence to link the presence of these antibodies with infusion reactions in particular or with AE's in general, with neutralization of the enzymatic activity of galsulfase, or with complement activation.

#### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical data source used to evaluate safety was clinical study reports and the datasets contained in the application. Table 50 lists the clinical studies reported in the application:

**Table 50. Clinical studies used in the evaluation of galsulfase safety**

| Study | Design | Study centers / subjects | Completion status / study dates | Treatment Doses | Duration of treatment | Number of participating subjects |
|---|---|---|---|---|---|---|
| 03-05 | Phase 3 Double-blind, randomized, placebo-controlled | USA: 6<br>Germany: 8<br>England: 6<br>Brazil: 8<br>France: 5<br>Portugal: 6 | Completed 7/21/03 to 4/8/04 | 1.0 mg/kg galsulfase once weekly vs. placebo | 24 weeks | galsulfase: 19<br>placebo: 20 |
| 03-06 | Phase 3 Open label, uncontrolled, extension to 03-05 | same as above | Ongoing | 1.0 mg /kg galsulfase once weekly | ongoing | galsulfase: 38 |
| 01-04 | Phase 2 Open label, uncontrolled | USA: 5<br>Australia: 5 | Ongoing (Report dates: 3/29/02 to 12/20/03) | 1.0 mg / kg galsulfase once weekly | Ongoing | galsulfase: 10 |
| 00-01 | Phase 1 / 2, double blind, randomized, dose comparison with open label extension | USA: 6<br>Austria: 1 | Double blind study complete. Extension study ongoing. (Report dates: 9/26/00 to 10/16/03) | 0.2 mg / kg vs. 1.0 mg/kg galsulfase once weekly Extension: 1.0 mg/kg | Ongoing | 0.2 mg/kg: 4<br>1.0 mg/kg: 3 |

7.2.1.1 Study type and design/patient enumeration

Please refer to Table shown in Section 7.2.1. Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety.

7.2.1.2 Demographics

| Study | Phase | Gender | Age range (years) | Race and Ethnicity |
|---|---|---|---|---|
| 00-01 | 1 / 2 | M 4 F 3 | 7 - 16 | 6 White<br>1 Black |
| 01-04 | 2 | M 3 F 7 | 6 -21 | 10 White |
| 03-05 | 3 | M 13 F 26 | 5 – 29 | 24 White<br>4 Hispanic<br>3 Black<br>2 Asian<br>2 Indigenous<br>4 Other |

7.2.1.3 Extent of exposure (dose/duration)

| Study | Phase | Dose | Duration | Number of Infusions |
|---|---|---|---|---|
| 00-01 | 1 / 2 | 3 subjects 1 mg / kg | 3 subjects 144 weeks<br>1 subject 85 weeks*<br>1 subject 75 weeks** | 588 |
| | | 4 subjects 0.2 mg / kg | 1 subject 3 weeks<br>1 subject 32 weeks<br>1 subject 59 weeks*<br>1 subject 69 weeks** | 159 |
| 01-04 | 2 | 10 subjects 1 mg / kg | 72 weeks | 717 |
| 03-05 | 3 | 19 subjects 1 mg / kg | 24 weeks | 437 |
| 03-06 | 3 (Ext) | 38 subjects 1 mg / kg | 24 weeks | 890 |

* 1 subject was switched from 0.2 mg / kg to 1 mg / kg at week 59 of Study 00-01
** 1 subject was switched from 0.2 mg / kg to 1 mg / kg at week 69 of Study 00-01

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources used to evaluate safety. BioMarin was the sponsor of all clinical studies under the IND 9057.

A letter from a sponsor-investigator conducting a "treatment" protocol in 2 siblings younger than age 5 is included in the application. — — , treated a 3 year old girl with MPS VI and her sibling, a 2 months old boy, with galsulfase for 8 and 11 months, respectively. There are no safety data contained in the letter, and the studies were not audited by BioMarin. Therefore, this sibling treatment protocol is not included in any safety analyses in this review.

### 7.2.2.1 Other studies

Not applicable, since there are no other studies beyond those described in the primary source of safety data, the biologic license application itself.

### 7.2.2.2 Postmarketing experience

There is no post-marketing experience with galsulfase.

### 7.2.2.3 Literature

Most of the recent literature references on galsulfase investigational treatment in MPS VI are related to the clinical studies described here. There are reports on bone marrow transplantation in patients with MPS VI, and these are also included in the application.

### 7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with galsulfase in the clinical development is as large as permissible given the constraints of the very low disease prevalence and the need to balance long term safety and efficacy data with the lack of adequate treatment for a condition that causes substantial morbidity and mortality. Sufficient drug exposure is reported and has been reviewed to allow a decision on licensing / approval for marketing. Due to the very small numbers of patients studied and the relatively short exposures for the majority of patients studied considering the lifelong need for the product, well designed, robust and rigorous studies will be needed as post-marketing commitments from BioMarin. These studies should include the evaluation of safety and efficacy of galsulfase in affected children younger than 5 years of age, the long term monitoring of safety and efficacy in the wider population of patients with MPS VI, and galsulfase activity, safety and efficacy in pregnancy and lactation.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The *in vitro* testing (for the characterization of the enzyme, determination of bioburden and contaminants, and demonstration of lysosomal uptake in MPS VI and normal fibroblasts) and animal toxicity studies were adequate to support the clinical development of galsulfase. The extensive use of the feline model of MPS VI was appropriate in narrowing the range of possible doses and schedules of administration of galsulfase to be developed in patients. Further clinical studies to optimize dose and dosing regimen exploration will be needed to ensure assessments in galsulfase bioactivity, as evidenced by urinary GAG concentrations, as well as efficacy in areas where no clinical benefit has been demonstrated but that are relevant to patients with MPS VI, such as benefits in respiratory capacity and cardiovascular parameters.

### 7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing planned and conducted in the studies supporting the application was adequate to comprehensively evaluate the safety of galsulfase.

The case report forms distributed to the clinical sites did not contain large boxes for investigator description of adverse events, so most common adverse events lack additional explanations that would be helpful in the consideration of MedDRA coding used by BioMarin. Nonetheless, there were enough data on adverse events for a review of safety in each of the clinical studies.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal drug-drug interactions studies were conducted in the development of galsulfase. This product is a biologic, which does not undergo metabolism and excretion in the same ways as small molecules do. Galsulfase has consistently been infused after administration of anti-histamines in the clinical trials reported in this submission. All safety information, therefore, is related to the concomitant use of anti-histamines and galsulfase. Corticosteroids, used rarely in

the clinical studies in those subjects that had experienced more severe infusion-associated reactions with prior galsulfase administration, can potentially mask the rise of anti-galsulfase antibodies. EMLA cream has been applied to the site for infusion to provide topical analgesia, and there is no evidence of a reaction between this product and galsulfase. No apparent drug-drug interaction was observed when galsulfase was administered concomitantly with the use of antibiotics or analgesic medications. Although the latter have been used frequently by subjects undergoing weekly infusions with galsulfase, the variety of antibiotics and analgesics used preclude a more robust analysis of any potential interactions.

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Galsulfase is the first product developed for the treatment of MPS VI, and can therefore be considered the first of its class. In a more general sense, safety issues related to intravenous infusions of a recombinant human enzyme have been identified in the studies supporting development of other products. This reviewer has evaluated the license application for a similar recombinant enzyme that is used the treatment of certain forms of MPS I (Hurler or Hurler-Scheie Syndrome). He is alerted to the likely allergic adverse events associated with such infusions. These adverse events were also noted in the development of galsulfase, being somewhat attenuated by pre-treatment with medications such as anti-histamines or glucocorticosteroids in specific situations. The evaluations were adequate.

Because the product is a therapeutic protein, assessments for immunogenicity potential are essential in the review of safety. Testing for immunogenicity at the timepoints proposed in the clinical protocol was adequate, even if the assays employed were not optimally robust. The testing for IgE and mediators of histamine release during infusion reactions was not as prevalent as one would desire, in order to understand the role of these mediators in the symptoms observed. Nonetheless, the frequency and severity of the infusion reactions have been defined in the clinical studies and in particular in the controlled study 03-05.

Further development of assays for anti-galsulfase immunoglobulins (both IgG and IgE) as well as testing for the allergic reactions markers such as serum tryptase are planned by BioMarin as post-marketing commitments.

### 7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data for review of safety was adequate. Please refer to previous comments made in this section 7.2.

### 7.2.9 Additional Submissions, Including Safety Update

All data related to the safety of galsulfase are contained within this application. BioMarin submitted the 120-Day Safety Update on March 29, 2005. The incremental data contained in the

Safety update appropriately included additional follow up on subjects currently receiving galsulfase in extensions of the 3 clinical studies. Specifically, the safety parameters are described and listed in datasets for weeks 194 through 204 in Study 00-012, for weeks 115 to 134 in study 01-04, and up to 51 weeks in the extension to Phase 3 study 03-06. The safety data includes AE's, SAE's, additional immunogenicity data, laboratory, physical examination and vital signs data related to the period included in the Safety Update.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

### 7.3.1 Infusion reactions

MPS VI patients, despite their young age, have very significant health problems that can confound the assessment of safety of galsulfase. The most useful assessment of safety in this population comes form the placebo-controlled study. From the adverse events that were observed during infusions, the following were more frequent in galsulfase-treated subjects as compared to placebo: Fever, rigors, headache, dyspnea and wheezing, nausea and vomiting, and rash and urticaria. Pain (including chest pain), headache and fatigue were also reported more commonly in galsulfase subjects during infusions but these were somewhat less specific and cannot be attributed with sufficient causality to galsulfase.

Other symptoms were more common with galsulfase than with placebo in Study 03-05. These are chest pain, abdominal pain, pharyngitis, conjunctivitis, ear pain, and hypertension. Clear attribution of causality of galsulfase for these adverse events is not feasible given the frequencies of these events and the likelihood that these events pertain to the background conditions of the subjects who exhibited them.

### 7.3.2 Immunogenicity

Anti-galsulfase antibody formation occurred in 98 % of subjects exposed to this product long enough to have an assessment of anti-galsulfase antibodies (53 of 54 subjects). No clinical evidence of neutralizing antibodies was observed in the studies conducted. This remains, however, a concern for these patients that need lifelong enzyme replacement, and high titers of neutralizing antibodies could affect the bioactivity and the clinical benefits of other enzyme replacement therapies to be developed in the future, whether in the form of alternate therapeutic recombinant human enzyme, gene therapies or replacement by bone marrow transplantation.

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

#### 7.4.1.1 Pooled data vs. individual study data

Data on frequent AE's has been pooled for the main analysis of adverse events under Section 7, Integrated Review of Safety. Where appropriate, comparative data related to safety within the placebo-controlled study are described.

#### 7.4.1.2 Combining data

When the data were pooled for the integrated analyses of safety the denominator was determined by adding the number of subjects in the 3 studies. For the most part, data from 56 subjects exposed to galsulfase were reviewed for laboratory, echocardiogram and ECG abnormalities, immunogenicity, AE's and SAE's, and deaths.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for dose dependency for adverse findings

Insufficient clinical data on subjects exposed to the 0.2 mg / kg dose exist to allow an adequate exploration of dose dependency for adverse events.

#### 7.4.2.2 Explorations for time dependency for adverse findings

Anti-galsulfase antibody formation was clearly time-dependent, as expected. Titers of antibodies rose from week 4 to week 48, then gradually decreased over the duration of the studies, and commonly fell below the limit of detection, suggesting tolerance to galsulfase over time. Infusion reactions were also time-dependent, occurring for the first time from Week 6 to Week 55.

#### 7.4.2.3 Explorations for drug-demographic interactions

There are no apparent interaction between the frequency and nature of adverse events and the demographic features of the subjects participating in the studies. The antibody titers appeared to be highest in those subjects with no detectable endogenous enzyme protein concentrations, but this demographic feature is not easily identifiable and the assay for ASB protein concentration and activity are not marketed assays available for general use.

#### 7.4.2.4 Explorations for drug-disease interactions

No drug-disease interactions were noted in the review of safety of galsulfase.

#### 7.4.2.5 Explorations for drug-drug interactions

See discussions above, under Section 7.2.6

### 7.4.3 Causality Determination

The limitations in the numbers of subjects exposed and the duration of exposure to galsulfase treatment in the context of a background of high frequency of multiple disorders related to MPS VI makes the determination of causality challenging, even in the placebo-controlled study. It appears that infusion reactions (these are extensively discussed in this and other sections of the review) are caused by galsulfase, as are the onset of anti-galsulfase antibody formation. Titers of anti-galsulfase IgG antibodies do not appear to be associated with frequency or severity of the infusion reactions, consumption of complement or in vivo neutralization of the sulfatase activity.

# 8 ADDITIONAL CLINICAL ISSUES

## 8.1 Dosing Regimen and Administration

The proposed dosing regimen, evaluated in Studies 01-04, 03-05 and 03-06, is 1 mg/kg/week by the intravenous route. BioMarin selected the galsulfase dose and dosing regimen on the basis of limited data: studies in the feline MPS VI model, in vitro studies of human fibroblasts, and a small dose-ranging study (Study 00-01). Study 00-01 provided the only clinical exploration of dose, wherein galsulfase doses of 0.2 mg / kg and 1 mg / kg administered once weekly by intravenous infusion, were compared. In this phase 1/2 study, only 4 subjects were randomized to the 0.2 mg/kg dose, and only 3 were randomized to the 1.0 mg/kg dose. One subject randomized to the 0.2 mg/kg dose cohort withdrew from the study before any assessment for bioactivity, and contributed essentially no data. Thus, data from only 3 subjects provide the sole clinical evidence in support of the concept that a lower Galsulfase dose would be associated with a less favorable risk-benefit relation than the proposed dose. The weight of data is particularly inadequate in view of the heterogeneity of the disease and variability of the treatment response.

Conversely, BioMarin did not explore doses higher than 1 mg/kg, such that the development program generated no data to support the concept that a higher dose would not provide a more favorable risk-benefit profile (presumably higher efficacy with acceptable safety).

Data from the feline model of MPS VI, as well as data from the clinical registration studies of laronidase in MPS I, suggest that these enzymes are taken up by disparate tissues and organs in different amounts, or that these enzymes exert heterogeneous activity across different tissues. For example, fibrous (cartilage-rich) tissues seem to be less affected by the enzyme than the reticulo-endothelial system, such as liver and spleen. Similarly the cornea appears to take up less enzyme or exhibit less enzyme activity that other tissues.

These examples suggest that the proposed dose of galsulfase may not be optimal / adequate:

- Four cats with MPS VI treated with recombinant human ASB from birth for 6 months exhibited less features of feline MPS VI than untreated cats; however, the cats exhibited persistent corneal clouding and joint disease (the enzyme was not detected in these tissues).
- A 2-month-old boy with MPS VI was treated with weekly galsulfase infusions for approximately 11 months. He maintained normal echocardiograms, audiograms, liver and spleen sizes on abdominal ultrasound, weight and linear growth rates. However, by Week 24, he had mild corneal clouding, and he exhibited significant rib cage flaring and pectus excavatum at the end of the treatment period.
- BioMarin conducted a study in cats with MPS VI investigating the combined effects of intravenous and intra-articular galsulfase administration in the prevention of degenerative joint disease (ASB-PC-008). BioMarin concluded that administration of a combination of intra-articular (500 $\mu$g / joint) and weekly intravenous dosing with galsulfase attenuated

joint-associated pathology in MPS VI cats compared to that observed in other studies in which cats received intravenous galsulfase therapy alone.

These data suggest that higher doses, and / or local administration of galsulfase, might improve efficacy.

The decision to continue development of galsulfase at a dose of 1 mg / kg / week was based, at least in part, from:

- Study 00-01 (despite the limited evidence of this being the best dose, as noted above)
- Results of 2 independent feline studies: Crawley et. al. assessed the effects of recombinant human N-acetylgalactosamine-4-sulfatase on urinary GAG excretion in MPS VI cats given 0.2 (n=1), 1 (n=3), or 5 (n=3) mg/kg/week (*J. Clin. Invest.* 1997;99:651). These investigators found evidence of a dose-response, based on urinary GAG and other parameters. Importantly, however, the 5 mg/kg dose did not normalize urinary GAG excretion. Higher doses were not studied.

  Subsequently, Bielicki et. al. studied the effects of feline N-acetylgalactosamine-4-sulfatase, 1 mg/kg/week, in 2 MPS VI cats (*J. Biol. Chem.*, 1999;274:36335), and compared their findings to the earlier results of Crawley et. al. Based on this historical comparison, Bielicki et. al. concluded that the 1 mg/kg/week regimen of feline enzyme had greater activity than the 1 mg/kg/week dose of human enzyme, and possibly "...as good as or better than the 5 mg/kg dose of human enzyme," potentially because of differences in antigenicity, glycosylation, or other factors. It is important to note, however, that the cats exhibited corneal clouding.
  Thus, the overall logic was:
  - The activity of 5 mg/kg human N-acetylgalactosamine-4-sulfatase was superior to 1 mg/kg or 0.2 mg/kg (in MPS VI cats); and
  - The activity of 1 mg/kg feline N-acetylgalactosamine-4-sulfatase was similar to that of 5 mg/kg of the human enzyme (in MPS VI cats).

  As such, a dose of 1 mg/kg seemed reasonable for clinical trials. Limitations inherent in this logic include small numbers of animals in each dosing cohort, the high variability in response, and the fact that the comparison between responses to feline and human N-acetylgalactosamine-4-sulfatase (in MPS VI cats) was historical. In addition, the studies did not seek or provide evidence that doses higher than 5 mg/kg/week would not have provided superior activity (i.e., evidence of maximal effect at 5 mg/kg). Finally, there are important limitations inherent in extrapolating animal data to human disease.

Despite these uncertainties in these conclusions, the investigators and BioMarin decided to pursue a 1 mg / kg weekly dose of the recombinant human enzyme in the clinical trials.

The decision to pursue a weekly dosing regimen is also based on animal data (Study ASB-PC-001), in which the tissue $t_{1/2}$ was 2-4 days in liver > spleen > lung > kidney > heart in 7 normal cats and in trials of weekly versus twice weekly infusions of galsulfase in MPS VI cats.

Given the low prevalence of the disease in humans, the pre-clinical and the clinical development were deemed to be reasonable. *However, there is little evidence that the dose and dosing regimen chosen for marketing is optimal for achieving benefits in children and adolescents*

*affected by MPS VI.* The sponsor should be encouraged to explore alternative dosages and dosing regimens, that could provide a superior risk-benefit relation.

## 8.2 Drug-Drug Interactions

No studies of drug-drug interactions were conducted. Please refer to Sections 1.3.5 and 7.2.6 for the reviewer's comments. All studies were conducted with pre-infusion treatment with intravenous or oral diphenhydramine (up to 1.25 mg / kg, not to exceed 50 mg) or equivalent anti-histamine.

## 8.3 Special Populations

The clinical studies were conducted in children older than 5 years of age and adolescents with MPS VI, with only a few adults. Therefore the safety and efficacy in children younger than 5 years of age and in older adults are unknown. Most study participants were Caucasian, possibly because of selection of sites where the investigator's expertise in MPS VI could be located. The analysis of 12 MWT and stair climb rate in Study 03-05 appears to indicate a significant difference in magnitude of the treatment effect between genders, favoring female subjects.

Evidence of the safety and efficacy in other age categories and racial / ethnic populations could be gathered from post-marketing studies or surveillance in registries.

Post-marketing studies or registries may provide data about any differential effects of galsulfase on endurance across genders.

## 8.4 Pediatrics

The clinical development program was conducted in children. Due to the requirement for subject cooperation in the assessment of the primary and secondary efficacy endpoints, children younger than 5 years of age were excluded. This is acceptable, as long as galsulfase safety and efficacy are studied in the younger patients as a post-marketing commitment prior to approval.

## 8.5 Advisory Committee Meeting

FDA decided not to convene a meeting of the Endocrinologic and Metabolic Advisory Committee to present the review of galsulfase for the treatment of patients with MPS VI. The decision was based on the experience with the development of laronidase, a recombinant human enzyme for the treatment of MPS I (Hurler, Hurler-Scheie or Scheie Syndrome), a condition that is very similar to MPS VI.

The clinical development and issues for galsulfase are very similar to the development of laronidase, which was presented to the Endocrinologic and Metabolic Advisory Committee. Laronidase was the first treatment ever approved for a Mucopolysaccharidosis condition, and the similarities between the 2 conditions (MPS I and MPS VI) and development programs made FDA comfortable making the appropriate regulatory decision without convening a meeting of the Advisory Committee.

## 8.6 Literature Review

Most of the literature references used in the review were provided by BioMarin, and the reviewer conducted searches in the references of the National Library of Medicine as appropriate. The main goal of the literature review was to enhance the knowledge of aspects of MPS VI, and the methods of assessments of the outcomes examined in the studies of galsulfase. Literature references were also used for a variety of reasons, from review of allergic reactions to infused proteins to basic science of lysosomal uptake though mannose-6-phosphate moieties.

## 8.7 Postmarketing Risk Management Plan

Postmarketing risk management plans are being discussed with BioMarin regarding galsulfase. The two core risk management programs intended for use of galsulfase in the commercial setting are Pharmacovigilance/ Safety Reporting and the Clinical Surveillance Program.

The Pharmacovigilance and Safety Reporting operations will be conducted in accordance with the appropriate regulations and guidelines for the monitoring of adverse events in patients receiving galsulfase. The Clinical Surveillance Program (CSP) is designed to enable the collection and analysis of the maximum amount of data regarding MPS VI and galsulfase treatment deemed to be reasonably collected in a voluntary, registry- like, commercial setting. The MPS VI CSP is intended to be an ongoing, observational database that tracks the specific clinical outcomes of patients with MPS VI disease, in particular those who receive galsulfase treatment. A protocol for this CSP is included in the application.

The CSP will be based on a protocol designed to evaluate the safety of long-term galsulfase administration and the specific areas of concern related to safety, such as negative effects of anti-galsulfase antibodies, management of infusion reactions and any interactions with other procedures to treat MPS VI patients, such as bone marrow transplantation. In addition, the long-term efficacy of galsulfase will be assessed through protocol-prescribed evaluations in the CSP.

## 8.8 Other Relevant Materials

After review of the proposed trade name [redacted] for the recombinant enzyme galsulfase under IND 9057, and consultation with the Division of Drug Marketing, Advertising and Communication (DDMAC) and the Division of Medication Errors and Technical Support (DMETS), the Division of Therapeutic Biologic Internal Medicine Products decided to reject that trade name. The objection was based on the determination that the name [redacted] Therefore, the name could misleadingly convey a unique effectiveness in [redacted], that have not yet been demonstrated through clinical studies. An alternative trade name proposed by BioMarin, "Naglazyme', was reviewed by DDMAC, DMETS and by our Division, and was found to be acceptable.

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

The conclusions of this review are tempered by 3 important realities:

- MPS VI is a progressive, debilitating and severe condition that causes death in children, adolescents and young adults;
- There is no effective treatment for the condition. Bone marrow transplantation has been used with some success, but is limited by the lack of suitable donors and is associated with a high degree of morbidity and mortality. Current treatment is supportive, directed to specific complications of MPS VI;
- MPS VI is a very rare disorder, with widely heterogeneous phenotypic presentations, that develops in affected individuals in different rates in disparate organs and tissues.

Efficay:

The selection of the distance walked in a 12-minute walk test as the primary demonstration of benefit came after discussion and agreement with FDA that this measure of physical endurance represents an integration of variable levels of improvement in systems such as locomotor, respiratory and cardiovascular. A study with a goal of demonstrating improved longevity, or a clinically significant effect in cardiovascular or respiratory parameters, although very desirable, would not be feasible within the context of the disease prevalence, heterogeneity of phenotypic presentation, and within a reasonable timeframe to complete the study.

BioMarin provided evidence of efficacy in the sample of subjects with MPS VI enrolled in the Phase 3 study, with an increment in the distance walked in the 12-minute walk test of approximately 90 meters, as compared to placebo. The baseline imbalance makes interpretation of the effect size difficult. Nevertheless, the methods and conclusions are statistically valid (See Statistical Review Document by Janice Derr, Ph.D.). The improvement in distance walked in the placebo-controlled Phase 3 study is supported by another, independent, measure of physical endurance, the rate of stair climbing in the 3-minute stair climb test. The impression of efficacy is further strengthened by data from the open-label extension of the double-blind study. In the extension study, all subjects received galsulfase. Thus, subjects who had received placebo in the controlled study were switched to active treatment; however, at the request of FDA, the subjects remained masked to their original treatment allocation in the double-blind study. After 24 weeks of open-label galsulfase treatment, they showed modest evidence of improvement in the 12 minute walk and stair climbing. Improvements were also observed in distance walked in subjects participating in uncontrolled studies, although evidence of enhanced endurance is actually expected under these circumstances, due to the importance of motivational factors and expectation bias. A substantial, rapid and durable reduction in urinary GAGs provides evidence for the bioactivity of galsulfase, potentially important in that the pathophysiology of MPS VI is due to the progressive accumulation of GAGs in lysosomes of many tissues and cells. Reduction

in urinary GAGs excretion is not shown to provide clinical benefit, but it might be interpreted as a marker of disease that may one day provide correlation with clinical benefits. BioMarin is currently conducting long term studies in MPS I in which subjects are being monitored by both urinary GAG and clinical parameters such as forced vital capacity and cardiac function. MPS I and the disease considered for treatment under this application, MPS VI, are distinct entities, but they share many pathophysiologic features.

Safety:

Similar to considerations for efficacy, safety considerations need to be tempered by 2 facts external to the merits of galsulfase itself:

- the severity of the disease (i.e., the risk of providing no specific treatment)
- the risks of exposing subjects to galsulfase against the benefits from the treatment.

Over 2000 adverse events were recorded in 56 subjects exposed to galsulfase in 3 studies. The majority of these can be traced to the manifestations of the disease itself.

The data raise two types of safety concerns related to galsulfase:

- Infusion reactions that range from a mild headache or flushing to a severe episode of apnea. BioMarin instituted an algorithm to reduce the frequency and severity of these reactions. All patients are pre-treated with anti-histamines. Although there is no demonstration in this development that the infusion reactions are histamine-mediated, there is support for experience in other therapeutic proteins, including laronidase in MPS I, that at least some reactions are accompanied by systemic histamine or tryptase release and are likely caused by these effectors of allergy and inflammation. Pre-treatment with anti-histamines did not eliminate infusion reactions, and these were far more common in subjects treated with galsulfase than those receiving placebo infusions. But the use of additional anti-histamines, slowing the rate of infusion, and addition of glucocorticosteroids to the regimen could be effective in decreasing the severity of the reactions. The safety database of the three clinical studies suggests that most subjects who experienced infusion reactions experienced a decrease in frequency and severity of reactions over time, even while the urinary GAGs remain decreased. Although this is an important concern that has to be taken into consideration in risk / benefit profile, the arguments above point to reasonable tolerability, without loss of efficacy.
- Anti-galsulfase antibodies were detected in all but one subject exposed to galsulfase treatment after a number of infusions were administered. We reviewed data in this application to correlate the antibody formation and titers to rate and severity adverse events, in particular infusion reactions, complement consumption leading to clinical manifestations, other allergic reactions, and evidence of neutralization of enzyme activity in vivo. Recognizing that the dataset is not robust, none of these analyses suggest that the presence or titers of anti-galsulfase IgG antibodies are associated with detrimental effects. In the post-marketing setting, BioMarin is expected to improve their assay for antibody detection, and continue to collect data on the potential effects of immunogenicity on safety and clinical benefits. A concern is that the development of neutralizing antibodies

could erase not only the potential benefits of galsulfase, but also those of newly developed forms of ASB replacement therapy, e.g., alternative therapeutic proteins, gene therapies, or improved bone marrow or cord blood transplantation.

## 9.2 Recommendation on Regulatory Action

This reviewer recommends approval of galsulfase for the indication of [redacted] in patients with Mucopolysaccharidosis VI (MPS VI). As documented in this review, the application contains sufficient data to support the efficacy of galsulfase. In addition, a clear pattern of both adverse events and immunogenicity potential related to galsulfase infusions emerged from the application, allowing an assessment of the risk - benefit profiles, and allowing for development of a label with adequate directions for use, under 21CFR § 201.5.

## 9.3 Recommendation on Postmarketing Actions

The efficacy and safety data in this application, while sufficient for approval of galsulfase, are insufficient to provide a full understanding of the long term effects of galsulfase treatment in the wider MPS VI population. So far, 250 patients with MPS VI have been identified worldwide. Sixty-five of these live in the United States. It is estimated that 1100 patients worldwide are affected by MPS VI. Major issues include gaining long-term safety and efficacy data, and exploring alternative dosages and regimens.

### 9.3.1 Risk Management Activity

Risk management will be primarily handled by Pharmacovigilance and post-marketing reports of safety information (in periodic or expedited reports). In addition, BioMarin proposes to sponsor a MPS VI Registry, where both the long-term efficacy and the safety of galsulfase treatment will be reasonably monitored.

### 9.3.2 Required Phase 4 Commitments

- **Registry study:** The evidence of efficacy was developed from a controlled study wherein there were eligibility restrictions regarding the distance walked at screening and the exclusion of patients who had undergone bone marrow transplantation. It is important to gather data on the efficacy of galsulfase in the general MPS VI population. In addition, it is important to collect long-term data on safety and efficacy of galsulfase treatment. Approval is based on the benefits demonstrated in less than 1 year treatment for the majority of study subjects, whereas the proposed treatment is life-long. Therefore, BioMarin should commit to the design and implementation of a Registry study for patients with MPS VI. The Registry should track the progress of all participating patients, whether treated with galsulfase or by other means, and should last 15 or more years. Periodic submission of Registry data to the

FDA for review and dissemination to interested parties is expected to provide the long-term data needed. Important parameters that contribute to the morbidity and mortality in MPS VI will need to be monitored periodically. A Clinical Surveillance Program protocol is included in the present BLA submission. Assessments are to be performed at regular, protocol-specified intervals, and include: urinary GAGs, height and weight, health resource utilization data, AE's and SAE's, mortality, proteinuria, antibody levels, endurance based on 12 minute walk tests and 3 minute stair climb, general appearance by photograph, neurologic assessments that include MRI's of the brain and spine, audiometric evaluations, ophthalmologic evaluations, electro- and echocardiographic assessments, pulmonary function tests and sleep studies, and liver / spleen size by physical exam and / or ultrasonography.

- **Additional dose and dose regimen exploration:** Dose and dosing regimen exploration during the development of galsulfase have been insufficient in providing evidence for optimal benefits. A study or studies to explore a range of doses and frequency of administration while assessing urinary GAGs and clinical endpoints is essential in ensuring that optimal clinical benefits are obtained from galsulfase.

The dose-finding study 00-01 described in this review explored only 2 doses of galsulfase, both given at weekly intervals. After 24 weeks into the dose comparison study, 2 of the original 4 subjects randomized to the lower dose (0.2 mg / kg) were changed to the higher dose of 1 mg/kg, while the other 2 subjects withdrew from the study. This limited dose exploration, is insufficient to address the optimal treatment of these patients. Two lines of reasoning support this assumption:

- [redacted] has been a sponsor-investigator of a study aimed at treatment of 2 very young subjects with MPS VI, a 3 7/12 year-old girl and her 2-month-old brother, respectively, [redacted] In reviewing the clinical data on the boy, we note that while his urinary GAGs were substantially reduced by 11 months of treatment with galsulfase, and other clinical parameters assessed have remained normal in this time period, corneal clouding was observed at Week 24. It is possible that this characteristic of MPS VI would affect the child regardless of the dose used, but it is also possible that a higher dose, or more frequent dosing, would allow galsulfase to enter the GAGs lysosomal deposits in the cornea and other tissues where progression of disease is observed.
- Results of 2 independent feline studies: Crawley et. al. assessed the effects of recombinant human N-acetylgalactosamine-4-sulfatase on urinary GAG excretion in MPS VI cats given 0.2 (n=1), 1 (n=3), or 5 (n=3) mg/kg/week (*J. Clin. Invest.* 1997;99:651). These investigators found evidence of a dose-response, based on urinary GAG and other parameters. Importantly, however, the 5 mg/kg dose did not normalize urinary GAG excretion. Higher doses were not studied.

  Subsequently, Bielicki et. al. studied the effects of feline N-acetylgalactosamine-4-sulfatase, 1 mg/kg/week, in 2 MPS VI cats (*J. Biol. Chem.*, 1999;274:36335), and compared their findings to the earlier results of Crawley et. al. Based on this historical comparison, Bielicki et. al. concluded that the 1 mg/kg/week regimen of feline enzyme

had greater activity than the 1 mg/kg/week dose of human enzyme, and possibly "...as good as or better than the 5 mg/kg dose of human enzyme," potentially because of differences in antigenicity, glycosylation, or other factors. It is important to note, however, that the cats exhibited corneal clouding.

Thus, the overall logic was:

The activity of 5 mg/kg human N-acetylgalactosamine-4-sulfatase was superior to 1 mg/kg or 0.2 mg/kg (in MPS VI cats); and

The activity of 1 mg/kg feline N-acetylgalactosamine-4-sulfatase was similar to that of 5 mg/kg of the human enzyme (in MPS VI cats).

As such, a dose of 1 mg/kg seemed reasonable for clinical trials. Limitations inherent in this logic include small numbers of animals in each dosing cohort, the high variability in response, and the fact that the comparison between responses to feline and human N-acetylgalactosamine-4-sulfatase (in MPS VI cats) was historical. In addition, the studies did not seek or provide evidence that doses higher than 5 mg/kg/week would not have provided superior activity (i.e., evidence of maximal effect at 5 mg/kg). Finally, there are important limitations inherent in extrapolating animal data to human disease..

In addition to limitations regarding the robustness of dose selections based on animals studied, the frequency of administration was not explored at all in human studies; the decision to conduct all clinical studies using a weekly infusion interval is based on a study that suggested the half life of recombinant human enzyme in selected tissues of MPS VI model cats had a 2-4 days range in selected tissues in 2 animals.

Given the low prevalence of the disease in humans, the pre-clinical and the clinical development were deemed to be reasonable. *However, there is little evidence that the dose and dosing regimen chosen for marketing is optimal for achieving benefits in children and adolescents affected by MPS VI.* Therefore we urge the to conduct a post-marketing dose-finding study exploring the risk-benefit profiles of higher dosages and / or a different schedule of administration.

- **Study in younger patients:** Even though MPS VI is usually diagnosed in the first several months of life, and there is evidence from the feline model of MPS VI that early therapeutic intervention with galsulfase is desirable, BioMarin's clinical development of galsulfase was done exclusively in subjects older than 5 years of age. Therefore, BioMarin needs to commit to the evaluation of galsulfase safety and efficacy in at least 10 patients with MPS VI who are younger than 5 years of age at the time of screening, and to follow such patients for at least 1 year. This evaluation can be a part of the Clinical Surveillance Program.

- **Pregnancy and lactation:** FDA does not expect that safety and efficacy of galsulfase use during pregnancy and lactation will necessitate a separate post-marketing commitment, but rather be studied as part of the MPS VI registry. This is due to the very low prevalence of the disease, and the very low probability that female subjects will become pregnant or breastfeed their infant.

### 9.3.3 Other Phase 4 Requests

- It would be valuable to study intra-articular galsulfase administration in the most severely affected joints, since the scant information we have is that galsulfase penetrates the articular space poorly with systemic administration. Galsulfase has been shown in the feline model to provide increased pharmacodynamic activity when injected in affected joints of MPS VI cats.
- It would be important for BioMarin to thoroughly study the nature of the infusion reactions that occur frequently with galsulfase treatment. BioMarin should develop an adequate assay for detection of anti-galsulfase IgE antibodies and subsequently use this assay in studies that monitor potential mediators of infusion reactions. In addition to IgE, assessment of serum tryptase and cytokines pre- and post-infusions may shed light on the nature of this infusion reactions, and measures to reduce their frequency and severity beyond the proposed routine use of anti-histamines.
- In addition, BioMarin needs to improve on the assays intended to measure ASB mass concentration and activity. Current assay vary substantially from laboratory to laboratory, and some measure either mass concentration or enzyme activity. Although the diagnosis of MPS VI is usually made through clinical phenotype combined with the urinary GAGs and specific substrates and genotypic analysis of mutations affecting enzyme concentration or activity in the majority of cases, additional homogeneous characterization of the enzyme deficiency may help characterize the patient population and factors related to safety, such as potential for immunogenicity, and efficacy in individual patients with MPS VI.

## 9.4 Labeling Review

This reviewer carefully reviewed the Section on Clinical Studies, Indications and Usage, Warnings, Precautions, Adverse Reactions, and Dosage and Administration. The recommended changes to the proposed labeling are as follows:

Clinical Studies:

- Only results from the placebo-controlled study and its open label extension need to be described here, as they provide the adequate evidence of efficacy for approval.
- The results tabulated in Table 1 and Table 2 (regarding results of the 12-Minute Walk Test and the Rate of Stair Climb, respectively) need to distinguish the difference in changes from baseline to week 24 between groups as that resulted form analyzes of the raw data from the analyzes of data adjusted for baseline. Preserving the data on median and quartile distributions is useful.
- There is no need to describe numerically the changes in urinary GAGs in the clinical study. A sentence to describe that urinary GAGs levels decreased in patients treated with galsulfase but not in patients treated with placebo is sufficient for this measure of bioactivity.
- The 12-minute walk and rate of stair climb data from the extension study 03-06 need to be briefly summarized in this Section, as they contributed to the strength of evidence of efficacy.

Indications:

- This section should be simply describe the patient population and state the fact that galsulfase has been shown to improve walking and stair climbing capacity.

Warnings (Infusion reactions):

- BioMarin included of the so called "anaphylactoid" reactions under the Warnings section. BioMarin needs to describe in this section all infusion reactions that are probably, likely, and certainly associated with galsulfase, regardless of the pattern of reactions or their recurrence. Although BioMarin had used the numbers related to anaphylactoid reactions, the labeling describes them . In addition, a concise and clear label must convey the likelihood of infusion reactions in a patient to be treated with galsulfase, even if the reaction does not recur. The number and proportion of reactions should be updated with the data from the open label extension, when those subjects originally randomized to placebo were noted to develop infusion reactions when switched to galsulfase treatment. As part of the Warning Section, the most severe symptoms associated with infusion reactions need to be emphasized from the most common symptoms. It is very important to briefly describe the recommended management in case of recurrent infusion reactions. In addition, it is important to state that there are no known predisposing factors that can predict infusion reactions.

Precautions (General):

- A specific recommendation to pursue the possibility of sleep apnea needs to be explicit in this section, for subjects being considered for galsulfase treatment. This is particularly important due to the pre-treatment with sleep-inducing anti-histamines and the risk for apnea during infusions.

Precautions (Information for Patients)

- BioMarin needs to include information for physicians and patients about the Clinical Surveillance Program, its goals and information on how to enroll.

Precautions (Pediatric Use):

- A statement should be deleted, as there is no evidence to support such statement.

Adverse Reactions:

- A statement describing the serious adverse reactions, the most common adverse reactions and the most common adverse reactions requiring interventions is missing from the proposed label. The listing of these reactions should be included under this section. Table 3 describing the adverse reactions should be simplified to contain only adverse events with a frequency in the galsulfase group greater than that of the placebo group by 2 or more subjects. Application of this rule, although using an arbitrary cutoff, may be more informative in describing common adverse reactions to be expected for galsulfase treatment.

Adverse Reactions (Infusion Reactions):

- Because all the label information on infusion reactions is included under the Warnings Section, this subsection of [redacted] can be deleted.

Adverse Reactions (Immunogenicity)

- The proportion of subjects who became anti-galsulfase antibody seropositive needs to be corrected and updated with the rates of antibody formation in the placebo-treated subjects who initiated treatment with galsulfase in Study 03-06. BioMarin included a patient treated for a short time before any assessments for antibody could be performed and included the subject as antibody negative.

  A statement about the immunogenicity data being dependent on the specificity and sensitivity characteristics of the assay, and the specimen handling or use of concomitant medications need to be included under this section.

Dosage and Administration:

- Information to providers regarding the possibility to extend the duration of infusions beyond 4 hours is helpful in this section. Duration of infusion has been extended up to 20 hours in the clinical studies, and several patients had their infusion temporarily interrupted to relieve the infusion reaction.

## 9.5 Comments to Applicant

The only comments to be conveyed to the applicant are those related to the labeling review and the post-marketing commitments that are required. No deficiencies precluding approval of galsulfase have been identified.

# 10 APPENDICES

## 10.1 Review of Individual Study Reports

### 10.1.1 Overview of the clinical studies:

The review of the safety and efficacy of galsulfase in patients with MPS VI is based on the study reports and the case report tabulations submitted under this license application. Two controlled studies (one dose-controlled and one placebo-controlled, with an uncontrolled extension) and one open-label, uncontrolled study, are the major components of this application. In addition, BioMarin conducted a cross-sectional survey of certain genetic and clinical characteristics of the MPS VI population, and has an expanded access program for 2 siblings who were ineligible to enter the aforementioned studies due to their young age. Please refer to Table 51 for a quick reference to the studies, reported individually in this section. Studies 03-05 and 03-06 were reviewed in Section 6. This section contains reviews of Studies 00-01 and 01-04.

**Table 51. Overview of Clinical Studies**

| Study | Design | Study centers / subjects | Completion status / study dates | Treatment Doses | Duration of treatment | Number of participating subjects |
|---|---|---|---|---|---|---|
| 03-05 | Phase 3 Double-blind, randomized, placebo-controlled | USA: 6<br>Germany: 8<br>England: 6<br>Brazil: 8<br>France: 5<br>Portugal: 6 | Completed 7/21/03 to 4/8/04 | 1.0 mg/kg galsulfase once weekly vs. placebo | 24 weeks | galsulfase: 19<br>placebo: 20 |
| 03-06 | Phase 3 Open label, uncontrolled, extension to 03-05 | same as above | Ongoing | 1.0 mg /kg galsulfase once weekly | ongoing | galsulfase: 38 |
| 01-04 | Phase 2 Open label, uncontrolled | USA: 5<br>Australia: 5 | Ongoing (Report dates: 3/29/02 to 12/20/03) | 1.0 mg / kg galsulfase once weekly | Ongoing | galsulfase: 10 |
| 00-01 | Phase 1 / 2, double blind, randomized, dose comparison with open label extension | USA: 6<br>Austria: 1 | Double blind study complete. Extension study ongoing. (Report dates: 9/26/00 to 10/16/03) | 0.2 mg / kg vs. 1.0 mg/kg galsulfase once weekly Extension: 1.0 mg/kg | Ongoing | 0.2 mg/kg: 4<br>1.0 mg/kg: 3 |

## 10.1.2 Study 00-01

### 10.1.2.1 Protocol

This was the first clinical study conducted in MPS VI subjects. It was a Phase 1 / 2, multicenter, double-blind, randomized, dose-controlled study. The original protocol was submitted on February 3, 2000. The protocol initially aimed to evaluate the safety, pharmacodynamic markers of MPS VI and pharmacokinetics of weekly infusions of galsulfase in patients with MPS VI in an open-label fashion, for a minimum of 3 months. The study design was changed to be a study comparing the safety and activity of a weekly dose of 0.2 mg / kg of galsulfase against a dose of 1 mg / kg galsulfase for 24 weeks. This initial period would then be followed by an extension study, where open-label weekly infusions would be offered to all subjects at a dose deemed to provide more evidence of bioactivity and safety.

Subjects to be included needed to be older than 5 years of age, have a documented diagnosis of MPS VI, confirmed through clinical signs and symptoms of the condition and a leukocyte ASB enzyme activity level that was less than 20 % of the normal range. The subjects also needed to demonstrate decreased endurance (decreased forced vital capacity, reduced joint range of motion and elevated urinary GAG's and hepatomegaly). Subjects would be excluded if they had undergone bone marrow transplantation.

Galsulfase infusions were given intravenously over a 4-hour period, after pre-treatment with anti-histamines and dilution of the galsulfase into 100 – 250 cc of normal saline.

The study monitored the safety aspects of the experimental treatment, but also assessed the distance walked in 6 minutes, the forced vital capacity, urinary GAG's, range of motion of both shoulders and knees, hepatomegaly, functional assessments as reported by the subjects in questionnaires, visual acuity and eye exam for corneal clouding, sleep studies, echocardiograms and electrocardiograms, and videotape of the subjects performing standard activities. These parameters were scheduled to be assessed at baseline, at week 13 and at the conclusion of the study.

### 10.1.2.2 Amendments

Amendment 1 was submitted on April 5, 2000. The main revisions were the change of the interim analysis from Week 6 to Week 12 and the ability of subjects to transfer to other investigational sites after the first 12 weeks of treatment.

Amendment 2 was submitted on June 15, 2000. It changed the protocol from an open label, single-dose study into a randomized, double-blind, 2-dose group study. A 0.2 mg / kg dose was added, in addition to the dose of 1 mg / kg. Procedures for randomization and blinding were instituted and described in the amendment.

Amendment 3 was submitted on January 20, 2001. The timing for the interim analysis was changed from Week 12 to Week 24.

Amendment 4 was submitted on November 12, 2001. The amendment, submitted after the interim 24 week analysis of the data, proposed placing all subjects on the 1 mg / kg dose. The results of the interim analyses were included in the amendment.

Amendment 5 was submitted on January 15, 2002. It delineated assessments to be performed in the participating subjects after week 72 of the study. In addition, the drug formulation was changed through the addition of – polysorbate-80. The new formulation was to be used in all subjects after they complete Week 84.

Amendment 6 was submitted on March 25, 2002. It altered the schedule of pharmacokinetic assessments to include both a Week 83 pharmacokinetic assessment as well as weeks 84 and 96. In addition, urinary GAG's, and antibody titers were to be determined at week 83, prior to the switch to the new formulation.

10.1.2.3 Post Hoc Changes

The main changes that were incorporated were the extension of study duration, and the change in the study design from an open-label single dose study to a randomized, double-blind, 2-dose study. The final statistical analytical plan was submitted on May 10, 2004, which included plans to analyze the data through week 144 of the study.

10.1.2.4 Results

*Disposition*

Seven subjects were enrolled in Study 00-01. Of these, 6 completed the initial 24 weeks of the study, and 5 completed 144 weeks of the study. The first subject was enrolled on September 26, 2000, and the last subject completed 144 weeks on October 16, 2003. Subject 40 (the first subject enrolled) withdrew from the study after Week 3 due to poor impulse control and danger to self and others. He had been randomized to the 0.2 mg / kg dose. Subject 50, also randomized to the 0.2 mg / kg dose, withdrew after 32 weeks in the study due to perception of lack of benefit. The remaining 5 subjects continued in the study through Week 144.

*Demographics*

The age ranged from 7 to 16 years of age (mean 11.6 ± 3.6 years). Four of the subjects were boys. The height of the subjects ranged from 86 to 150 cm (mean 107.5 ± 21.6 cm). The weight ranged from 15.5 to 43 kg (mean 23.3 ± 9.3 kg). Six were Caucasian and one was African American.

*Baseline Characteristics*

Urinary GAGs excretion ranged from 70 to 520 μg / mg creatinine (mean 323 ± 360 μg / mg creatinine).

Other baseline characteristics are shown in Table 52

**Table 52. Baseline characteristics of subjects in Study 00-01**

| Subject | Dose (mg/kg) | Leukocyte ASB (μg / mg protein)* | Ventilatory assistance | Corneal clouding | Visual impairment | Sleep Apnea | Joint Stiffness | Joint Contracture |
|---|---|---|---|---|---|---|---|---|
| 40 | 0.2 | 16 | None | Mild | Mild | None | Moderate | Moderate |
| 41 | 0.2 | 6 | None | Mild | Mild | None | None | Mild |
| 45 | 0.2 | 18 | Trach | Moderate | Moderate | Resolved with trach | Mild | Moderate |
| 50 | 0.2 | 16 | Trach, CPAP, BiPAP at night | None (post corneal transplant) | None | None | Mild | Severe |
| 42 | 1 | 13 | None | Moderate | None | Mild | Moderate | Moderate |
| 43 | 1 | 15 | Nasal O2 at night | Moderate | Severe | Moderate | Severe | Severe |
| 44 | 1 | 13 | Trach, CPAP, BiPAP with URI | Moderate | Severe | Resolved with trach | Severe | Severe |

* Normal range for leukocyte ASB protein concentration varies among laboratories.

The genetic mutations and amount of ASB protein, as well as activity of ASB in vitro correlated poorly with the severity of the clinical manifestations. Twelve different genetic mutations in the ASB gene were identified in the 7 subjects enrolled. Three mutations resulted in premature termination of the peptide, bringing about little or no enzyme activity. In one of them, subject 41, the highest level of urinary GAG excretion was identified, but the functional impairment was overall classified as mild to moderate.

*Efficacy*

**10.1.2.4.1.1 Efficacy Endpoints**

*Reviewer comment: The protocol for this study did not specify which of these endpoints are primary, secondary and exploratory. This is acceptable in a pilot study, as the main goal of a "first in man" is usually the ascertainment of safety and possibly pharmacokinetics, while looking for early effects on pharmacodynamic, or bioactivity markers.*

10.1.2.4.1.1.1 Results of the first 24 weeks: dose finding portion of the study:

- Urinary GAGs and dermatan sulfate: The normal range for urinary GAGs in children aged 3 to 12 years is 25 to 71 μg / mg creatinine and in children aged 13 to 18 it is 7 to 38.5 μg / mg creatinine. Table 53 shows individual baseline and Week 24 urinary GAGs levels in subjects participating in Study 00-01.

**Table 53. Urinary GAGs in subjects receiving 2 doses of galsulfase in Study 00-01**

| Subject | Age | Galsulfase Dose (mg/kg) | Urinary GAGs (μg / mg creatinine) | | % Change |
|---|---|---|---|---|---|
| | | | Baseline | Week 24 | |
| 41 | 7 | 0.2 | 520 | 153 | - 71 |
| 45 | 11 | 0.2 | 158 | 90 | - 53 |
| 50 | 13 | 0.2 | 379 | 188 | - 50 |
| 42 | 7 | 1.0 | 218 | 105 | - 52 |
| 43 | 16 | 1.0 | 500 | 107 | - 79 |
| 44 | 12 | 1.0 | 416 | 88 | - 79 |

Although it is clear that subjects had reductions in the levels of urinary GAGs, the % change in urinary GAGs had no clear relation to the dose used.

There were parallel decreases in the levels of urinary dermatan sulfate. The % reduction in dermatan sulfate levels in the urine ranged from – 53 % to – 87 %.

- 6-Minute walk test: Table 54 shows the distances walked in the 6-minute walk test (6 MWT) at baseline and at week 24 in study 00-01.

**Table 54. 6 MWT distances walked by subjects in Study 00-01**

| Subject | Galsulfase Dose (mg/kg) | Distance walked in 6 MWT (meters) | | % Change |
|---|---|---|---|---|
| | | Baseline | Week 24 | |
| 41 | 0.2 | 197 | 213 | 8 |
| 45 | 0.2 | 283 | 325 | 15 |
| 50 | 0.2 | 133 | 143 | 7 |
| 42 | 1.0 | 388 | 355 | - 8 |
| 43 | 1.0 | 53 | 152 | 187 |
| 44 | 1.0 | 89 | 151 | 71 |

Similar to the urinary GAGs, the data regarding the 6 MWT shows some increases in distance walked from baseline to Week 24, but the inter-subject variability of the results precludes any conclusion on a dose-response.

- Shoulder flexion and extension: The normal mean (± SD) for shoulder flexion for the children 6 –12 years of age is 169 (± 3.5) degrees and for shoulder extension it is 69.6 (± 7.0). These values are provided for comparison to those observed in subjects 41, 45, 42 and 44. The normal mean (± SD) for adolescents aged 13 – 19 years is 167.4 (± 3.9) and 64.0 (± 9.3) for shoulder flexion and extension, respectively. These values are provided to be used in comparison to those observed in subjects 50 and 43. Please refer to Table 55 for the data on shoulder range of motion (ROM).

**Table 55. Shoulder flexion and extension ROM in subjects treated with galsulfase in Study 00-01**

| Subject | Dosage (mg/kg) | Shoulder Flexion ROM (degrees) | | | | | | Shoulder Extension ROM (degrees) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Wk 0 | | Wk 24 | | % Change | | W 0 | | Wk 24 | | % Change | |
| | | L | R | L | R | L | R | L | R | L | R | L | R |
| 41 | 0.2 | 99 | 92 | 97 | 100 | -2 | +9 | 50 | 50 | 68 | 68 | +36 | +36 |
| 45 | 0.2 | 92 | 89 | 97 | 90 | +5 | +1 | 70 | 62 | 64 | 66 | -9 | +6 |
| 50 | 0.2 | 64 | 48 | 73 | 67 | +14 | +40 | 46 | 48 | 53 | 49 | +15 | +2 |
| 42 | 1.0 | 113 | 117 | 119 | 119 | +5 | +2 | 36 | 27 | 56 | 54 | +56 | +100 |
| 43 | 1.0 | 79 | 83 | 92 | 91 | +16 | +10 | 53 | 62 | 62 | 63 | +17 | +2 |
| 44 | 1.0 | 75 | 85 | 88 | 88 | +17 | +4 | 34 | 38 | 40 | 38 | +18 | 0 |

It is clear from the study that all subjects studied had limitations in either shoulder flexion or extension or both, as compared to normal children. BioMarin pointed out that improvements in flexion and extension in at least 1 shoulder was noted in all 6 subjects after 24 weeks of treatment with galsulfase. However, the intra- (left and right and the screening vs. Week 24) and inter-subject data on shoulder range of motion are so variable, that no conclusion on an effect of galsulfase is possible from the study.

- Grip and Pinch Strength: results of these 2 tests among the subjects in both dose cohorts were inconclusive, as there were substantial variability even within the same individual with increases in grip strength in one hand and decreases in the other hand over the first 24 weeks of the study.

- Pulmonary function tests: except for Subject 40, who withdrew early from the study and who had normal forced vital capacity (2.77 L) and forced expiratory volume (2.43 L) at screening, all other subjects in both dose groups had very poor respiratory capacity (range of FVC 0.3 to 0.95 L and range of FEV1 0.30 to 0.67 L) and did not demonstrate any clinically significant changes over the 24 weeks of the study. Three of the subjects had tracheostomies and their pulmonary function assessments were made through the tracheostomies.

- Childhood Health Assessment Questionnaire: The pain score is subjectively reported on a scale from zero (no pain) to 100 (very severe pain). Three subjects had decreases in pain scores (-37, -75 and – 20), while one subject on the 1 mg / kg galsulfase treatment had an increase in pain score (+25), and 2 subjects had no change. The arthritis score also ranges from zero (very well) to 100 (very poor). Four subjects had a decrease in scores (-30, -25, - 70, and – 55), and one had no change. The disability index, ranging from zero (no disability) to 3 (severe disability), showed inconclusive results, with little or no variation among all subjects.

*Reviewer comment: Although all the conclusions of efficacy that can be derived from Study 00-01 are limited by small sample size and the wide spectrum of disease severity, assessments such as these patient-reported outcomes are the most subject to bias, and therefore the least valuable from the standpoint of objective efficacy evaluations.*

- Cardiac function: No significant changes were detected in any of the subjects in the ECG or echocardiographic findings from baseline to Week 24.

- Visual exam findings: Although all subjects had abnormalities under the slit lamp at baseline, no changes were observed in the 24 weeks of treatment in either dose group. No changes were observed in the fundoscopic examination and intraocular pressure.

- Sleep studies: These evaluations were performed in the 3 subjects who did not have tracheostomies. Two of them did not experience any changes in the 24 weeks of the study, and the third (subject 43) had worsening of the Apnea Hypopnea Index at week 24, that was determined to be related to administration of a narcotic prior to the sleep study.

- CT scan of the liver: Due to inconsistencies and non-reproducibility of the findings of hepatomegaly in historical reports in MPS VI, liver volumes were estimated by CT scan, and the proportion of liver weight to total body weight was calculated and compared to normative data adapted from Stocker and Dehner, 1992. Two subjects had hepatomegaly at baseline according to the normative data employed, and these had small reductions in liver volume relative to body weight at Week 24: subject 50 had a reduction from 3.4 to 2.9 % of body weight and subject 43 had a reduction from 3.8 to 3.3 % of body weight). The other subjects had normal liver volumes that remained normal over the first 24 weeks of the study.

- Bone mineral density, cervical spine and chest X-ray results: no clinically significant differences were observed in these assessments through the first 24 weeks of Study 00-01.

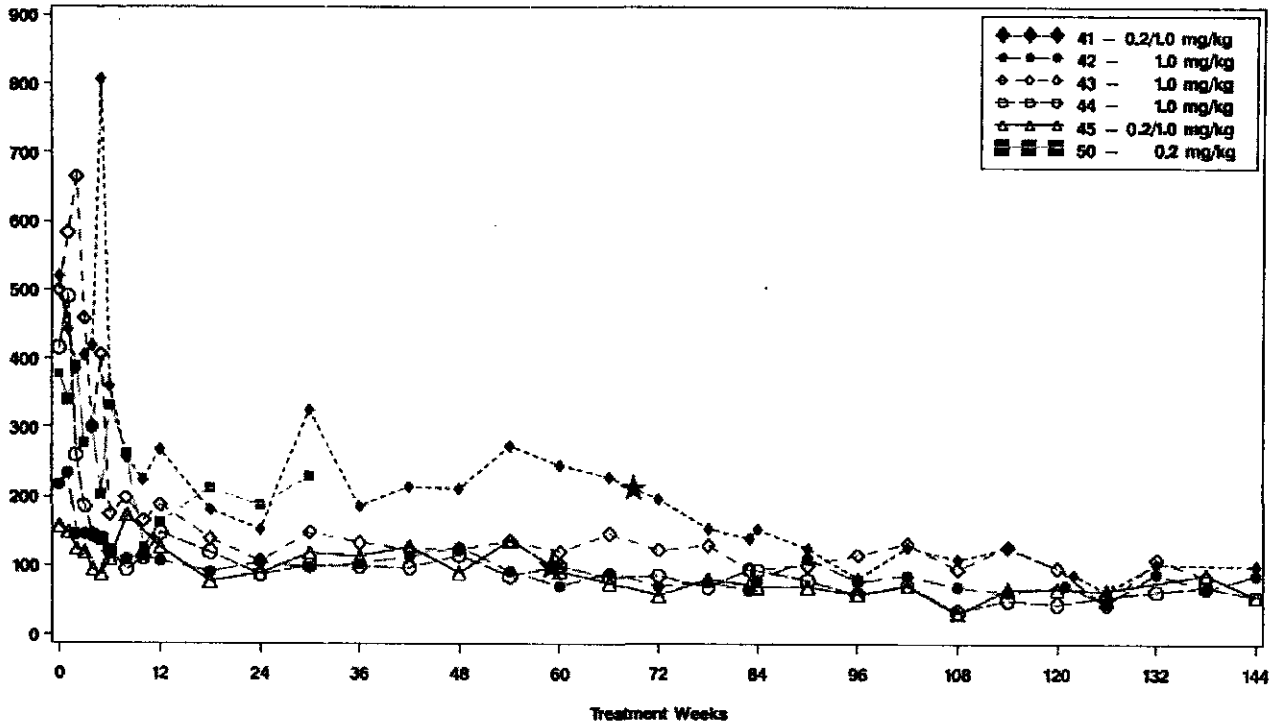
- Height and weight: Gain in height ranged from 0.5 to 1.8 inches, and weight increase was modest, except for subjects 44 and 45 who gained 9.5% and 8.3 % by week 24, compared to baseline.

*Reviewer comment: The changes reported are probably not clinically or statistically significant, but they are difficult to interpret without an appropriate normative background for pubertal stage and for age-related growth rate.*

10.1.2.4.1.1.2 Results through Week 144: open label extension

- Urinary GAGs and dermatan sulfate: The initial reduction in urinary GAG s was maintained through week 144. The 2 subjects initially randomized to the 0.2 mg / kg weekly dose of galsulfase experienced further reduction in urinary GAGs and dermatan sulfate after their treatment dose was increased to 1 mg / kg, on weeks 59 and week 69. The urinary GAGs over time in the 144 weeks of this study are shown in the Figure 13, adapted from BioMarin's figure 14.2 – 1.

**Figure 13. Urinary GAGs in subjects treated with galsulfase for 144 weeks in Study 00-01**




- 6-Minute walk test:

**Table 56. Distances walked in the 6 MWT (meters) through 144 weeks of study 00-01**

| Subject | Galsulfase dose (mg/kg) | Wk 0 | Wk 24 | Wk 48 | Wk 144 |
|---|---|---|---|---|---|
| 41 | 0.2 | 197 | 213 | 204 | 289 |
| 45 | 0.2 | 283 | 325 | 408 | 398 |
| 50 | 0.2 | 133 | 143 | Subject withdrew | |
| 42 | 1 | 388 | 355 | 408 | 624 |
| 43 | 1 | 53.1 | 152 | 179 | 176 |
| 44 | 1 | 88.7 | 151 | 126 | 92.3 |

Subject 50 dropped out of the study at week 32, so no assessments were made at Week 48 or Week 144. Of the 5 remaining subjects, 4 had increases ranging from 40 % to 231 % of baseline (the absolute increase in distance walked from baseline to week 144 varied from 92 to 235 meters in these 4 subjects). Subject 44, who had shown a 63 meter increment from baseline (71% increase) at Week

24, had no change in distance walked as compared to baseline by Week 144. This could be attributable at least in part to back pain, neck pain and neurological symptoms that resulted in C1-C3 decompression surgery at Week 92 of the study.

- Mean shoulder flexion / extension: All 5 subjects that remained in the study extension had improvements in shoulder flexion ranging from 13 to 24 degrees at week 144. Shoulder extension demonstrated more variability, with 2 subjects showing improvement (14 and 26 degrees) and 3 subjects showing unchanged shoulder extension at week 144 compared to baseline (-1 to – 8 degrees).

- Grip and pinch strength: Subjects have shown little or no change in grip strength through the 144 weeks reported in this study report.

- Pulmonary function: No significant changes in FVC or in FEV1 were observed during the 144 weeks of study, as compared to baseline pulmonary function in all subjects. Subjects 42 and 45 had improvements in FVC (over 10 % from baseline) that coincided with increases in height after week 96. Subject 43 also had a 10 % increase in FVC that coincided with a 26 % reduction in liver volume over the first 96 weeks of the study. These increments in FVC, however, are clinically small, ranging from 50 to 100 mL.

- Childhood health assessment questionnaire: Except for subject 41, the arthritis score and pain scores improved from baseline to Week 144 in the 5 remaining subjects. The disability index scores were unchanged from baseline to Week 144.

- Cardiac function: No electrocardiographic or echocardiographic changes were seen in any of the subjects through Week 144.

- Visual exams: No changes in fundoscopic or slit lamp results were seen in any of the 5 subjects that remain in the study through Week 144. None had changes in intra-ocular pressure. Three subjects had improvements in visual acuity in both eyes, but the magnitude and clinical impact of these improvements are small.

- Sleep studies: The 3 subjects who did not have tracheostomies at screening underwent sleep studies at protocol-specified intervals during the study. These 3 subjects had obstructive sleep apnea at baseline that remained relatively constant through Week 144, with the apnea / hypopnea index remaining relatively unchanged from baseline to Week 144, as well as the proportion of sleep time spent with oxygen saturation less than 90 %.

- CT scan of the liver: Even though the liver volumes increased, liver as percent of body weight decreased by 0 – 0.7 %. Subject 43 who had hepatomegaly at baseline had the largest reduction in liver volume, both absolute (10 % decrease) and relative to body weight (0.7 %).

- Height and weight changes: Three subjects had small increases and 2 subjects had small decreases in height (the subjects that were more severely affected at baseline, subject 43 and 44).

- Chest and cervical spine X rays: No clinically significant changes were seen.

### 10.1.2.4.1.2 Pharmacokinetic endpoints

10.1.2.4.1.2.1 Studies at weeks 1, 2, 12 and 24

Of the 4 subjects in the 0.2 mg / kg cohort, one (subject 41) had high levels of anti-galsulfase antibodies that interfered with the ELISA assay, and the levels of ASB were always below the limit of quantitation. Another subject (subject 40) left the study before the weeks 12 and 24 pharmacokinetic assessments.

$AUC_{0-t}$ remained relatively constant through week 24, in the range of 10,000 to 13, 800 min · ng / mL. For the 3 subjects in the 1 mg / kg cohort, the $AUC_{0-t}$ increased from week 1 to week 2, and remained constant at week 12. At week 24 subject 43 had shown an increase in $AUC_{0-t}$ that corresponded to high titer of antibodies at that timepoint. The same subject had pharmacokinetic assessment at week 83 with $AUC_{0-t}$ that declined toward the mean for the group, coinciding with a drop in antibodies from 4.6 OD/μL to 1.4 OD/μL).

*Reviewer comment: Two subjects (41 and 43) developed antibodies to galsulfase, with completely opposite effects on the assay measurement of serum ASB concentrations. It is not clear that the interference with the ELISA assay could indicate any biologic implication of one antibody type versus another.*

10.1.2.4.1.2.2 Studies at weeks 83, 84 and 96

Starting at Week 84, subjects received a new formulation incorporating ~ polysorbate 80. Pharmacokinetic studies were repeated to assess the comparability between the 2 formulations. Although there was significant overlap between the pharmacokinetic parameters estimated from the Week 83 and Weeks 84 and 96 studies, there appeared to be an increase in AUC0-t and a decrease in total body clearance with the polysorbate formulation (Table 57).

**Table 57. Pharmacokinetic outcomes measured at weeks 83, 84 (polysorbate 80 added), and 96 in Study 00-01**

| Parameter | Week 83 | Week 84 | Week 96 |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 1143 ± 284 | 1367 ± 262 | 1341 ± 523 |
| $T_{max}$ (min) | 180 | 120 | 121 |
| $AUC_{0-t}$ (min· ng / mL) | 172,400 ± 50,000 | 213,700 ± 45,800 | 200,000 ± 76,500 |
| CL (mL/min/kg) | 6.23 ± 2.1 | 4.81 ± 1 | 5.54 ± 2.1 |
| $V_z$ (mL/kg) | 67.6 ± 22 | 122 ± 60 | 123 ± 17 |
| $V_{ss}$ (mL/kg) | 266 ± 52 | 236 ± 21 | 233 ± 28 |
| $t_{½}$ (min) | 8.5 ± 4.7 | 19 ± 13.2 | 17.3 ± 8.3 |
| MRT (min) | 44.4 ± 7.6 | 50.9 ± 12.9 | 46.1 ± 16.1 |

*Reviewer comment: BioMarin notes that there is overlap among the values for $AUC_{0-t}$ and clearance between the studies conducted at Week 83, on the one hand, and Weeks 84 to 96, on the other hand, where comparing the galsulfase formulation pharmacokinetic properties before and after addition of polysorbate 80 to the formulation. However, we can see consistent increases in both $AUC_{0-t}$ and $t_{½}$ with the new formulation, and some decrease in clearance. BioMarin also tried to make the case that the plasma half life and plasma AUC are not a good measure of drug exposure to the target tissue lysosomes, and BioMarin estimates that mannose 6 phosphate lysosomal receptors are saturated with galsulfase with the doses employed in the study. We conducted a small analysis of a pharmacodynamic effect, namely effect of galsulfase on urinary GAGs, only in those 3 subjects (subject 42, 43 and 44) that were initially*

*randomized to 1 mg / kg and maintained the same dose throughout the 144 weeks of the study, and looked at the 4 timepoints where urinary GAG where measured prior to the implementation of the formulation change (Weeks 66, 72, 78 and 83) and at the 4 timepoints at the end of the study period (Weeks 126, 132, 138, and 144) and observed the following: subject 42 had urinary GAGs reduced from 76 to 73 µg / g creatinine, subject 43 had urinary GAGs reduced from 124 to 64, and subject 44 had urinary GAGs reduced from 84 to 62 µg / g creatinine. We do not anticipate any implications from this minor increase in exposure on the clinical efficacy, since the efficacy study 03-05 was conducted using the new galsulfase formulation containing polysorbate 80.*

**10.1.2.4.1.3 Safety**

10.1.2.4.1.3.1 Exposure

Of the 7 subjects, 6 completed the initial 24 weeks of the study, and 5 completed 144 weeks of the study. Subject 40 discontinued participation after week 3 and subject 50 discontinued participation after week 32. Subjects 43, 44 and 45 missed 2 infusions out of 144 and subject 41 missed 1 infusion. A total of 159 weekly infusions were given at 0.2 mg / kg and 588 weekly infusions were given at 1 mg / kg during the study period.

10.1.2.4.1.3.2 Adverse Events

BioMarin defined infusion associated reactions (IAR's) as adverse events that occurred during infusion and were considered to be possibly, probably or definitely related to the study drug. "Anaphylactoid" reactions were defined by BioMarin as IAR's that occur during multiple infusions or that improve with decreased infusion rate, interruption of infusion and/or treatment with additional anti-histamines or steroids.

Baseline through Week 24: Seventy-five of the 86 AE's reported are unrelated to study drug and reflect the underlying spectrum of symptoms and signs present in patients with MPS VI. No patient discontinued the study due to AE's. The rate of AE's was not different between the 4 subjects randomized to 0.2 mg / kg and the 3 subjects randomized to 1 mg/ kg (34 in the 0.2 mg / kg and 53 in the 1 mg / kg), and were minor (rash, urticaria, etc). The only severe AE was depression in subject 40, that was noted in the Medical History before participation in the study, and was the reason for dropping out. IAR's were: 2 events of hypotension in subject 50 (0.2 mg / kg cohort). Rash occurred in subject 43 and was considered an "anaphylactoid" reaction, that did not require changes in infusion and / or concomitant medications.

Week 25 through Week 144: The 4 patients initially randomized to the 0.2 mg / kg cohort experienced a cumulative total of 159 AE's and the 3 subjects in the 1 mg / kg cohort had 261 AE's. The most common AE's were related to symptoms of upper respiratory infections (otitis media, sinusitis and cough) which are prevalent in this patient population. Of the 420 AE's during this phase of the study, 367 (87%) were considered unrelated to study drug, and 86 % were considered mild and 12 % considered moderate. Of the severe AE's, subject 40 developed a brain glioma (also considered SAE) and bilateral carpal tunnel syndrome, subject 41 had a seromucotympanum, subject 44 had umbilical hernia and spinal cord compression and respiratory distress. All of these severe AE's were considered to be unrelated to the study drug. The only death in the study was of subject 40, who had received 3 infusions of galsulfase at 0.2 mg / kg. At 10 months after dropping out of the study [redacted], the subject was diagnosed with brain glioma (further defined as glioblastoma multiforme – astrocytoma grade 4) and 4 months later [redacted] with colon cancer. He died in [redacted] The combination of these neoplasias suggested

Turcot Syndrome (familial adenomatous polyposis with CNS tumors). The subject had a comprehensive genetic mutational analysis and was found to have a deleterious germline mutation in the MSH2 gene, with premature truncation of the MSH2 protein at amino acid 81.

10.1.2.4.1.3.3 Anti-galsulfase antibodies

5 of the 6 subjects remaining in the study beyond Week 3 (thus excluding subject 40), developed antibodies to galsulfase. The highest levels were observed in subject 41 (in the 0.2 mg / kg cohort), with rapid rise from baseline to Week 24 (11.4 OD/ µL serum) , then rapid decline until Week 66, then becoming undetectable from Week 126 to Week 144. The second highest rise was observed in subject 43 (1 mg / kg cohort), with increase to 4.6 OD/ µL serum by Week 24 and to 7 OD/ µL serum at Week 60. The other subjects had variable rises in antibody titers with peak between Weeks 36 and Week 48, then decreasing to near the detection limit of the assay at 0.2 OD/ µL serum. No evidence of complement depletion was observed. There were no relationships between onset of detection of antibodies or their titers and reduction of urinary GAG's, IAR's and other adverse vents.

10.1.2.4.1.3.4 Clinical laboratory findings and vital signs

No clinically significant changes were observed in these parameters.

10.1.2.5 Conclusions

This was the first galsulfase study in man, and was designed as a dose finding study in the target population.

While galsulfase clearly demonstrated reductions in urinary GAGs that persisted for 144 weeks, this endpoint cannot be readily viewed as a surrogate for efficacy:

- correlation between urinary GAGs levels and severity of disease at baseline was poor
- no independent demonstration of correlation between reduction of urinary GAGs and clinical benefits.

The study provided limited evidence of benefit in clinical endpoints, particularly the distance walked in a standardized 6-minute walk test.

- This endpoint was used by BioMarin in the study of patients with MPS I to support the efficacy of the enzyme therapy in that similar condition.
- A dose response was not shown, possibly due to the small sample size and wide inter- and intra-subject variability of distances walked.
- Improvement in distances may be related to expectation bias, rather than a treatment effect.

The safety parameters in the study were appropriately monitored, and included a collection and review of adverse events, anti-galsulfase antibody formation, and clinically significant laboratory and physical examination changes from baseline. While all subjects exposed to galsulfase for longer than 3 weeks developed antibodies, there is no indication

that the effect on urinary GAGs or other parameters of clinical benefit were adversely affected by presence or the titers of those antibodies.

Conclusions of this study are somewhat limited by the sample size and variable severity of the subjects, the fact that ascertainment of changes in some important endpoints (such as the 6 minute walk test) could be affected by the knowledge of the treatment used (no placebo arm was tested). On the other hand, a positive aspect of this study is the long term monitoring of patients under treatment and demonstration of continuous reduction of urinary GAGs, as well as lack of evidence of significant deterioration of these subjects during the 2 years of study treatment.

10.1.2.6 Summary

Study 00-01 was a small study, intended for assessment of the safety and bioactivity of galsulfase, with the investigation of 2 doses of the product. This was also the first study of galsulfase in humans. It was designed as a randomized, double-blind, dose controlled, 2-center for 24 weeks. The 2 doses tested were the 0.2 mg / kg and the 1 mg / kg, both of these given as intravenous 4-hour infusions at weekly intervals. The study monitored the safety aspects of the experimental treatment, but also assessed the distance walked in 6 minutes, the forced vital capacity, urinary GAGs, range of motion of both shoulders and knees, hepatomegaly, and other outcomes. BioMarin analyzed the results of urinary GAGs and the clinical endpoints from the first 24 weeks, and concluded that all subjects would benefit from treatment with 1 mg / kg dose. 7 subjects were enrolled and randomized. The first subject enrolled withdrew from the study after the third infusion of galsulfase 0.2 mg / kg and his replacement (in the same dose cohort) withdrew from the study after 32 weeks. The remaining 2 subjects in the 0.2 mg / kg dose cohort were switched to treatment with 1 mg / kg weekly on weeks 59 and 69 into their study.

Results: Urinary GAGs decreased in all subjects: the 3 subjects treated with galsulfase 0.2 mg / kg over the 24 weeks was between 40 and 70 % from the baseline while for the 3 subjects treated with galsulfase at 1 mg / kg over 24 weeks the urinary GAGs decreased from 50 to 80% from their baseline values. The urinary GAGs in the 2 subjects initially treated with 0.2 mg / kg decreased further over time while on the 1 mg / kg dose, to 65 to 90 % decrease from baseline.

Five subjects had variables improvements in distance walked from 10 to 99 meters during the first 24 weeks of the study. From the 144 weeks of data on this test in study 00-01, the absolute increase in distance walked from baseline to Week 144 varied from 92 to 235 meters in the 4 subjects of the 5 subjects remaining after Week 32, while the fifth subject who had improvements in the first 24 weeks developed severe neurologic complications and had a decrease in distance walked by Week 144.

Other tests, such as shoulder flexion and extension, grip and pinch, pulmonary function, questionnaires, echocardiograms, sleep studies showed inconclusive results. Subjects with mild hepatomegaly at baseline had a small reduction in liver volume. By Week 144, shoulder flexion improved in all 5 subjects. Other tests showed results that were largely unchanged and inconclusive.

The results of the safety analysis through the 144 weeks of the study were significant for the death of the first subject enrolled in the study (from malignancy) for reasons unrelated to galsulfase use. Most adverse events were likely related to complications of MPS VI, although infusion reactions (primarily rash and urticaria) were observed in subjects in both dose cohorts.

### 10.1.3 Study ASB-01-04

(Review conducted by Dr. Anne Pariser)

#### 10.1.3.1 Protocol

This study was an open-label pharmacokinetic (PK), efficacy, and safety study of weekly infusions of galsulfase 1 mg/kg in 10 subjects (7 females, 3 males) with MPS VI.

Subjects were to have been 5 years of age or older at study entry, with documented MPS VI (biochemical or genetic diagnosis) and the ability to walk at least 1 meter (m), but no more than 250 m in the first 6 minutes of the 12-Minute Walk Test at baseline. Subjects were excluded if they had undergone bone marrow transplantation (BMT). Subjects were enrolled and had efficacy evaluations performed at 1 of 2 primary treatment centers, 1 in the United States (n=5) and 1 in Australia (n=5).

Subjects received weekly infusions of galsulfase for the first 6 weeks at the primary treatment centers, then could receive treatment closer to home (at a local center) thereafter. There were no concomitant medication restrictions during the study, except for other investigational medications.

Subjects were evaluated at the primary treatment center weekly for 6 weeks, and at Weeks 12, 24, 48 and 72. The primary endpoints of the study were measurements of endurance and mobility, and urinary GAGs levels. Endurance and mobility testing included: the 12-Minute Walk Test (12MWT), the Stair Climb Test, the Expanded Timed Get-Up-and-Go Test (ETGG), shoulder range of motion (ROM), Grip and Pinch Strength tests, pain and joint stiffness questionnaires, and MPS VI Quality of Life (QoL) Profile. Secondary endpoints included measures of PK, safety, physical activity, oxygenation during sleep, bone density, liver and spleen size, echocardiograms, pulmonary function tests (PFT's), visual exams, and linear growth. The study visits and procedures are summarized in Table 58 and Table 59:

**Table 58.Study ASB-01-04: Study Visits and Procedures, Baseline through Week 24**

| **Study Period** | **Baseline** | | | **Treatment Weeks** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **-2 to 0** | | | **1** | **2** | **3** | **4** | **5** | **6** | **8** | **12** | **18** | **24** |
| **Location** | P | P | P | P | P | P | P | P | P | L | P | L | P |
| **Procedure** | | | | | | | | | | | | | |
| Sign Informed Consent | X | | | | | | | | | | | | |
| **Confirmation of MPS VI Diagnosis** | | | | | | | | | | | | | |
| Leukocyte ASB | | X | | | | | | | | | | | |
| Fibroblast | | X | | | | | | | | | | | |
| **Efficacy Measurements** | | | | | | | | | | | | | |
| ETGG | X | X | | | | | | | XX | | XX | | XX |
| Shoulder Joint ROM | | X | | | | | | | X | | X | | X |
| Stair Climb | X | X | | | | | | | XX | | XX | | XX |
| 12MWT | X | X | | | | | | | XX | | XX | | XX |
| Grip & Pinch Strength | | X | | | | | | | X | | X | | X |
| QoL Profile | | X | | | | | | | X | | X | | X |
| Child/Adult Questionnaire | | X | | | | | | | X | | X | | X |
| **Safety Measurements** | | | | | | | | | | | | | |
| Medical History | | X | | | | | | | | | | | |
| Physical Exam | | X | | X | | | | | X | | X | | X |
| MPS VI Signs & Symptoms | | X | | | | | | | X | | X | | X |
| Antibody Testing | | X | | X | | | X | | X | X | X | X | X |
| Complement Test | X | X | | XX | | | | | XX | | XX | XX | XX |
| ECG | | X | | | | | | | | | X | | X |
| Safety Labs | X | X | | X | | | | | X | | X | X | X |
| Thyroid Panel | | X | | | | | | | | | | | |
| PK Assessment | | | | X | X | | | | | | X | | X |
| **Other Measurements** | | | | | | | | | | | | | |
| Physical Activity | | X | | | | | | | X | | X | | X |
| $O_2$ Sat during Sleep | X | X | | | | | | | | | XX | | XX |
| CT scan (bone density and liver & spleen size) | | X | | | | | | | | | | | |
| Echocardiogram | | X | | | | | | | | | | | |
| PFT's | X | X | | | | | | | | | | | XX |
| Visual Exam | | X | | | | | | | | | | | |
| Urinary GAGs | X | X | X | X | | | X | | X | X | X | X | X |
| Urinalysis | | X | | X | | | | | X | | X | X | X |
| Sleep Study (Australia only) | | X | | | | | | | | | | | X |

P = Primary Center, L = Local Center
XX = to be completed twice on separate days, pre- and post-infusions

**Table 59.Study ASB-01-04: Study Visits and Procedures, Weeks 25 through 72**

| Study Period | Treatment Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Week** | **30** | **36** | **42** | **48** | **54** | **60** | **66** | **72** | **ET** |
| **Location** | L | L | L | P | L | L | L | P | P |
| **Procedure** | | | | | | | | | |
| **Efficacy Measurements** | | | | | | | | | |
| ETGG | | | | XX | | | | | X |
| Shoulder Joint ROM | | | | X | | | | | X |
| Stair Climb | | | | XX | | | | | X |
| 12MWT | | | | XX | | | | | X |
| Grip & Pinch Strength | | | | X | | | | | X |
| QoL Profile | | | | X | | | | | X |
| Child/Adult Questionnaire | | | | X | | | | | X |
| **Safety Measurements** | | | | | | | | | |
| Physical Exam | | X | | X | | X | | X | X |
| MPS VI Signs & Symptoms | | | | X | | | | X | X |
| Antibody Testing | X | X | X | X | X | X | X | X | X |
| Complement Test | | | | XX | | | | XX | X |
| ECG | | | | X | | | | | X |
| Safety Labs | | X | | X | | X | | X | X |
| Thyroid Panel | | | | X | | | | | X |
| **Other Measurements** | | | | | | | | | |
| Physical Activity | | | | X | | | | | X |
| $O_2$ Sat during Sleep | | | | XX | | | | | X |
| CT scan (bone density and liver & spleen size) | | | | X | | | | | X |
| Echocardiogram | | | | X | | | | | X |
| PFT's | | | | XX | | | | XX | X |
| Visual Exam | | | | X | | | | | X |
| Urinary GAGs | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X | X | X |
| Sleep Study (Australia only) | | | | X | | | | | X |

P = Primary Center, L = Local Center
XX = to be completed twice on separate days

10.1.3.2 Amendments

There were 3 amendments to the study.

Amendment 1 was submitted 31-January-02, and the main revisions were to alter inclusion, exclusion and withdrawal criteria, and to change the frequency and performance of some of the efficacy and safety measures. Amendment 2 was submitted 29-March-2002, and the main revisions were changes and clarifications to some of the efficacy measures. Amendment 3 was submitted 04-August-2003, and the main revisions were updates of study sites and personnel, and clarifications to some of the study procedures. None of the amendments changed the overall design or conduct of the study. In addition, there were 4 amendments to the statistical plan, all of which were minor.

10.1.3.3 Protocol Deviations

The most common protocol deviations were missed or delayed protocol-specified collection times for safety and efficacy assessments (most commonly lab tests). The majority of deviations were minor and were unlikely to have effected the overall study results. However, deviations in the performance of the Grip Strength and Pinch Strength tests, in which different equipment was used in the assessment of 4 of 10 subjects in the Grip Strength test and 5 of 10 subjects in the Pinch Strength test, likely introduced variability in the results of these tests making interpretation of the results difficult (see Efficacy Results below). Two additional protocol deviations related to study inclusion criteria in 2 subjects (Subjects 301 and 304) and resulted in exceptions being authorized for these subjects. Subject 301 was discovered to have significant sleep apnea requiring continuous positive airway pressure (CPAP) support. After stabilization on CPAP for 3 weeks, the screening tests were repeated and all inclusion criteria were met. Subject 304 had glaucoma that could have required surgery and an exception was made to include this subject. It is doubtful that either of the 2 exceptions meaningfully impacted the results or interpretation of the study.

10.1.3.4 Results

*Disposition*

Ten subjects were enrolled in the study: 5 subjects in the US and 5 subjects in Australia. Subjects were entered and participated in the study between 22-March-2002 (first patient signed the Informed Consent) and 20-December-2003 (last patient completed the 72-week infusion). No subject withdrew from the study or was discontinued, and all 10 subjects received study drug through Week 72.

*Demographics*

There were 7 female and 3 male subjects enrolled in the study. At baseline, subject ages ranged from 6 to 21 years, all subjects were Caucasian, and urinary GAGs levels ranged from 138 to 518 μg/mg creatinine (Cr) (normal range: 50.5 μg/mg Cr in 4-6 year olds to 11.1 μg/mg Cr in >18 year olds). As is typical of MPS VI, all subjects were of short stature for age, with height ranging from 85 to 125 cm (33 to 49 inches). The baseline demographic data are summarized in the following table.

**Table 60. Study ASB-01-04, Baseline Demographics**

| Subject | Age (years) | Gender | Urinary GAGs Level (μg/mg Cr) | Height (cm) | Weight (kg) | Race |
|---|---|---|---|---|---|---|
| 200 | 17 | F | 361 | 96 | 20 | Caucasian |
| 201 | 8 | M | 342 | 93 | 20 | Caucasian |
| 202 | 16 | F | 247 | 120 | 33 | Caucasian |
| 203 | 14 | F | 347 | 107 | 30 | Caucasian |
| 204 | 6 | F | 519 | 87 | 15 | Caucasian |
| 300 | 21 | F | 422 | 102 | 21 | Caucasian |
| 301 | 9 | M | 187 | 122 | 32 | Caucasian |
| 302 | 6 | M | 434 | 100 | 19 | Caucasian |
| 303 | 8 | F | 361 | 85 | 15 | Caucasian |
| 304 | 16 | F | 138 | 125 | 29 | Caucasian |
| **Mean (SD)** | **12 (5)** | - | **336 (116)** | **104 (14)** | **23 (7)** | - |

*Baseline Characteristics*

The disease characteristics of the subjects at baseline were consistent with the underlying disease. Baseline characteristics were notable for all 10 subjects having short stature, corneal clouding, joint stiffness, and joint contractures. Nine subjects had restrictive lung disease or obstructive airway disease, 9 subjects had visual impairment, 6 subjects had hearing impairment, and 3 subjects had sleep apnea. The baseline disease characteristics are summarized in the following table.

**Table 61.Study ASB-01-04, Baseline Disease Characteristics**

| Subject | Short Stature | Hearing Impairment | Restrictive Lung Disease | Corneal Clouding | Visual Impairment | Sleep Apnea | Joint Stiffness | Joint Contracture |
|---|---|---|---|---|---|---|---|---|
| 200 | + | + | + | + | + | + | + | + |
| 201 | + | + | + | + | 0 | + | + | + |
| 202 | + | 0 | + | + | + | 0 | + | + |
| 203 | + | + | + | + | + | 0 | + | + |
| 204 | + | 0 | + | + | + | 0 | + | + |
| 300 | + | 0 | + | + | + | 0 | + | + |
| 301 | + | + | + | + | + | 0 | + | + |
| 302 | + | + | 0 | + | + | + | + | + |
| 303 | + | + | + | + | + | 0 | + | + |
| 304 | + | 0 | + | + | + | 0 | + | + |

+ = present, 0 = absent

Five subjects had neurological features of MPS VI, including communicating hydrocephalus (n = 4, Subjects 200, 302, 303 and 304), cervical spine instability (n = 2, Patients 302 and 304), and spinal disc disease (n = 2, Subjects 300 and 303). Four subjects (Patient 201, 301, 303 and 304) utilized CPAP, variable positive air pressure (VPAP), or bi-level positive air pressure (BiPAP) support (no subject had a tracheostomy). All subjects had cardiac valve abnormalities.

A full analysis of genetic mutations and biochemical characterization of residual enzyme activity was performed for all subjects. There were a total of 20 mutations identified that potentially cause pathology, 6 of which have been described in the literature. Of these 6 mutations, 5 are known to contribute to the most rapidly advancing clinical presentation, which is consistent with the advanced clinical presentation of the majority of subjects in the study. Subject 303 was noted to be homozygous for a null mutation (null phenotype) with premature termination of the ASB polypeptide. No ASB protein was detected in this subject's fibroblasts, nor was any enzyme activity (above background level) detected. The level of ASB activity did not show perfect correlation with actual clinical phenotype. Subjects 202, 301 and 304 had an intermediate clinical presentation relative to the other 7 subjects, yet only Subject 301 had a relatively high level of enzyme. Subject 202 had a very high protein level, but the basis for this had not been determined.

*Efficacy*

**10.1.3.4.1.1 Primary Efficacy Endpoints**

The primary efficacy endpoints were change from baseline in measures of endurance and mobility, including:

- 12-Minute Walk Test (12MWT)
- Stair Climb Test
- Expanded Timed Get-up and Go Test (ETGG)
- Shoulder Joint Range of Motion (ROM)
- Grip and Pinch Strength Tests
- Childhood and Adult Pain and Joint Stiffness Questionnaires
- MPS VI Quality of Life (QoL) Profile

10.1.3.4.1.1.1 12-Minute Walk Test (12MWT)

The 12MWT is a measure of endurance, and has been shown to be a reproducible and useful test of exercise tolerance in patients with cardio-respiratory disease.[1,2] No literature was located (by this Reviewer or by the sponsor) on the use of the 12MWT in MPS VI or for other diseases caused by inborn errors of metabolism. It is noted that an increase of 54m (95% CI of 37-71 m) in the 6MWT is considered to be a clinically relevant improvement in lung disease patients[3], but no cutpoint of clinically relevant improvement appears to have been established for the 12MWT for any group of patients. The 6-Minute Walk Test (6MWT) was performed in Study ASB-00-01, but it was felt by the sponsor to under-represent the daily limits of endurance for MPS VI and a "training effect" was seen. Therefore, the 12MWT was selected by the sponsor for this study as it was felt to be more sensitive to total distance walked than to walk speed, and may detect smaller increments of improvement in a patient population with multiple

1 McGavin CR, Gupta SP, McHardy GJR. Twelve-minute walking test for assessing disability in chronic bronchitis. BMJ 1976;1:822-823.
2 Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. BMJ 1982;284:1607-1608.
3 Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997;

functional deficits contributing to limitations in endurance, including cardiovascular (CV), pulmonary and joint mobility.

The 12MWT was performed 2 times on separate days at baseline (Weeks -2 to 0) and at Weeks 6, 12, 24 and 48 (at baseline the shortest distance walked in the first 6 minutes of the two 12 MWT s was collected for eligibility). Subjects were instructed to walk as far as possible in 12 minutes. A stopwatch was used to time the test, and distance walked was recorded at 6 and 12 minutes. No verbal encouragement could be given to the subjects during the test. The same enclosed corridor was used for all tests within each primary center. Subjects could use the wall as a guide, but no assist devices were permitted.

The results showed that there was a wide range of distances walked among subjects at baseline, Week 6, Week 24 and Week 48 in the 6-minute and 12-minute time intervals. All subjects increased the distance walked at Week 48 compared to baseline in the 6-minute and 12-minute intervals, and in general, most subjects showed progressive increases in distance walked at each visit through Week 48. Change at Week 48 ranged from +6 m to +237 m at 6 minutes (mean +91 m), and +47 m to +595 m at 12 minutes (mean +211). The 2 subjects with the 2 highest baseline 12MWT scores showed the smallest increases in distance walked at Week 48 (Subject 301 walked 475 m at baseline and 595 m at Week 48 [+120], and Subject 204 walked 472 m at baseline and 519 m at Week 48 [+47]). The 3 subjects with the lowest baseline 12MWT scores had the 4th, 6th and 7th largest increases in distance walked at Week 48. The 4 subjects with the highest baseline 12MWT scores (Subjects 202, 302, 204 and 301) also had the lowest percent increases in 12MWT, and the 3 subjects with the lowest baseline 12MWT scores had 3 of the 4 highest percent increases in 12MWT.

The distance walked in 6 minutes and 12 minutes at baseline and Weeks 6, 24 and 48 are shown for each subject in Table 62.

**Table 62.Study ASB-01-04; 12MWT Results at Baseline and Weeks 6, 24 and 48**

| | Baseline (m) | | Week 6 (m) | | Week 24 (m) | | Week 48 (m) | | Change at Week 48 (m) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Subject | 6 Min | 12 Min | 6 Min | 12 Min | 6 Min | 12 Min | 6 Min | 12 Min | 6 Min | 12 Min |
| 200 | 19 | 33 | 52 | 88 | 66 | 126 | 83 | 156 | +64 | +123 |
| 201 | 138 | 254 | 104 | 178 | 198 | 384 | 286 | 536 | +148 | +282 |
| 202 | 215 | 410 | 275 | 513 | 318 | 618 | 330 | 644 | +115 | +234 |
| 203 | 84 | 146 | 109 | 181 | 97 | 185 | 140 | 266 | +57 | +120 |
| 204 | 247 | 472 | 204 | 398 | 226 | 478 | 252 | 519 | +6 | +47 |
| 300 | 101 | 101 | 71 | 71 | 142 | 242 | 146 | 280 | +46 | +180 |
| 301 | 245 | 475 | 264 | 491 | 314 | 595 | 308 | 595 | +64 | +120 |
| 302 | 221 | 435 | 162 | 371 | 300 | 598 | 310 | 618 | +90 | +183 |
| 303 | 85 | 101 | 138 | 250 | 119 | 216 | 174 | 330 | +89 | +229 |
| 304 | 172 | 215 | 353 | 698 | 384 | 753 | 408 | 810 | +237 | +595 |
| **Mean (SD)** | **152 (79)** | **264 (170)** | **173 (99)** | **324 (205)** | **216 (109)** | **419 (219)** | **244 (103)** | **475 (207)** | **+91 (64)** | **+211 (152)** |

The results at baseline and Week 48, Change at Week 48, and percent change at Week 48 are also organized in ascending order by baseline 12MWT results in the following table.

**Table 63.Study ASB-01-04, 12MWT Results in Ascending Order by Baseline 12MWT Scores**

| | Baseline (m) | | Week 48 (m) | | Change at Week 48 (m) | | % Change at Week 48 | |
|---|---|---|---|---|---|---|---|---|
| Subject | 6 Min | 12 Min | 6 Min | 12 Min | 6 Min | 12 Min | 6 Min | 12 Min |
| 200 | 19 | 33 | 83 | 156 | +64 | +123 | +334% | +378% |
| 300 | 101 | 101 | 146 | 280 | +46 | +180 | +45% | +179% |
| 303 | 85 | 101 | 174 | 330 | +89 | +229 | +104% | +227% |
| 203 | 84 | 146 | 140 | 266 | +57 | +120 | +68% | +82% |
| 304 | 172 | 215 | 408 | 810 | +237 | +595 | +138% | +277% |
| 201 | 138 | 254 | 286 | 536 | +148 | +282 | +108% | +111% |
| 202 | 215 | 410 | 330 | 644 | +115 | +234 | +53% | +57% |
| 302 | 221 | 435 | 310 | 618 | +90 | +183 | +41% | +42% |
| 204 | 247 | 472 | 252 | 519 | +6 | +47 | +2% | +10% |
| 301 | 245 | 475 | 308 | 595 | +64 | +120 | +26% | +25% |

The data are also represented graphically in the following figures for the first 6 minutes walked and for the full 12MWT:

**Figure 14. Study ASB-01-04, Distance Walked in 6 Minutes from Baseline to Week 48**

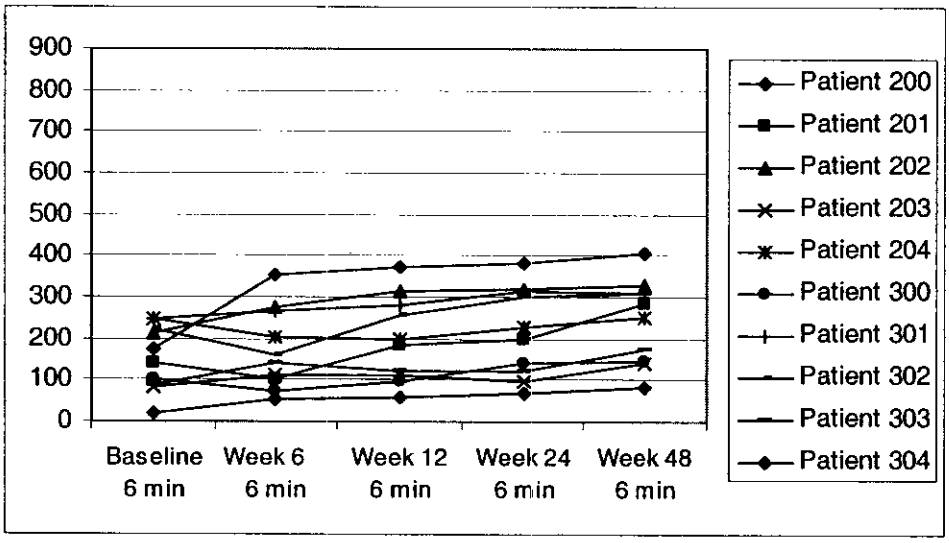
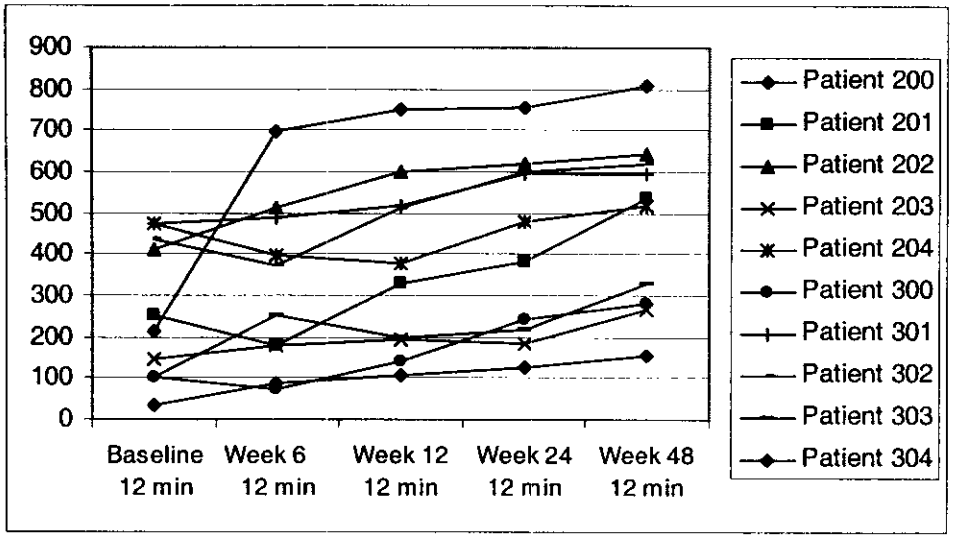


**Figure 15. Study ASB-01-04, Distance Walked in 12 Minutes from Baseline to Week 48**




All subjects showed increases in distance walked from baseline in the 12MWT although treatment response was quite variable. Subjects with the lowest scores at baseline had the highest percent increases in distance walked, and subjects with the highest baseline scores had the lowest percent increases. Some of the increases may be attributed to conditioning or a training effect, which may have been an important factor in this test.

It is noted that the 12MWT was performed twice for each visit on different days, and in all cases and at every visit the distance walked in the second test was greater than or equal to the distance walked in the first test. In some cases, the distance walked in the second test was more than twice the distance of the first test. For example, the mean of the distance walked for all first tests was 204m, and for all second tests was 394 m; a mean percent increase of 95% for the second test over the first test.

Nonetheless, as MPS VI is a progressive disease that would be expected to show deterioration rather than improvement over the 48-week treatment period, the results are at least suggestive of an improvement in endurance with treatment. No definite conclusions can be established from these findings, however, as the study was small and uncontrolled, a training effect was seen, and no cutpoints for clinically relevant improvement have been established for this population of patients for either the 6MWT or the 12MWT.

### 10.1.3.4.1.1.2 Stair Climb Test

The Stair Climb test is another measure of endurance, and has been used as a screening test (prior to surgery) in patients with chronic respiratory disease to estimate cardiopulmonary reserve.[4,5] In chronic respiratory disease patients, the number of steps climbed correlates with pulmonary function tests, but is also an indicator of other parameters (e.g., CV status, cooperation).[5] However, no previous data correlating to patients with MPS VI or other diseases caused by inborn errors of metabolism are available for this test.

4 Pollock M, Roa J, Benditt J, Celli B. Estimation of ventilatory reserve by stair climbing. A study in patients with chronic airflow obstruction. Chest 1993;104:1378-1383.
5 Bolton JWR, Weiman DS, Haynes JL, Hournung CA, Olsen GN, Almond CH. Stair climbing as an indicator of pulmonary function. Chest 1987;92(5):783-788.

The Stair Climb Test was performed 2 times on separate days at baseline and at Weeks 6, 12, 24 and 48. Subjects were timed for 3 minutes while going up the stairs, and the total number of steps going up was recorded. The same stairs were used at all visits, and no verbal encouragement or physical assistance could be given.

The results showed a wide range of stairs climbed per subject at baseline (24 to 92 stairs, mean 50) and at each week tested. In general, subjects showed progressive increases in stairs climbed at each visit through Week 48. All subjects increased the number of stairs climbed at Week 48 compared to baseline, with increases ranging from +2 to +136 stairs (mean +61). The greatest percent increase in stairs climbed was in the subject with the smallest number of stairs climbed at baseline, but unlike the 12MWT, the change from baseline and the percent change from baseline did not otherwise correlate well with baseline score. In addition, as the Stair Climb test was performed twice on separate days, a comparison was made between the Day 1 and Day 2 tests to see if a "training effect" could be seen (as was seen for the 12MWT). Unlike the 12MWT, there was no consistent increase in the number of stairs climbed on Day 2 from Day 1; however, a training effect over the duration of the study could not be ruled out. The results at baseline and Weeks 6, 12, 24 and 48 are summarized in the following table.

**Table 64. Study ASB-01-04, Stair Climb Test Results**

| Subject | Number of Stairs Climbed in 3 Minutes | | | | | Change at Week 48 |
|---|---|---|---|---|---|---|
| | Baseline | Week 6 | Week 12 | Week 24 | Week 48 | |
| 200 | 24 | 40 | 41 | 45 | 49 | +25 |
| 201 | 20 | 53 | 72 | 91 | 112 | +92 |
| 202 | 79 | 96 | 104 | 116 | 116 | +38 |
| 203 | 30 | 40 | 34 | 36 | 52 | +23 |
| 204 | 91 | 75 | 85 | 94 | 103 | +12 |
| 300 | 28 | 22 | 32 | 31 | 30 | +2 |
| 301 | 92 | 114 | 116 | 180 | 204 | +112 |
| 302 | 67 | 77 | 84 | 182 | 198 | +132 |
| 303 | 22 | 37 | 25 | 34 | 60 | +39 |
| 304 | 50 | 122 | 155 | 174 | 185 | +136 |
| **Mean (SD)** | **50 (30)** | **67 (35)** | **75 (43)** | **98 (63)** | **111 (65)** | **+61 (51)** |

The results at baseline and Week 48, Change at Week 48, and percent change at Week 48 are also organized in ascending order by baseline Stair Climb test results in the following table.

**Table 65. Study ASB-01-04, Stair Climb Test Results in Ascending Order by Baseline Result**

| Subject | # of Stairs Climbed in 3 Minutes | | Change at Week 48 | % Change at Week 48 |
|---|---|---|---|---|
| | Baseline | Week 48 | | |
| 201 | 20 | 112 | +92 | +460% |
| 303 | 22 | 60 | +39 | +179% |
| 200 | 24 | 49 | +25 | +102% |
| 300 | 28 | 30 | +2 | +9% |
| 203 | 30 | 52 | +23 | +76% |
| 304 | 50 | 185 | +136 | +274% |
| 302 | 67 | 198 | +132 | +198% |
| 202 | 79 | 116 | +38 | +48% |
| 204 | 91 | 103 | +12 | +13% |
| 301 | 92 | 204 | +112 | +121% |

The sponsor further evaluated the data by correlating the results of the Stair Climb test with the results of the 12MWT by rank order (largest to smallest scores) based on change (increase) from baseline at Week 48. Although both tests measure endurance, only 5 of 10 subjects had similar rank orders in both tests. These results suggest that the 2 tests may be measuring different aspects of endurance, such as the CV, pulmonary, mobility, or functional components of endurance.

Additionally, similar to the 12MWT, although all subjects showed increase in the number of stairs climbed, the magnitude of the improvement was quite variable. No specific conclusions can be reached from these findings as the study was small and uncontrolled, a training effect cannot be ruled out, and there are no accepted standards of improvement with this test in any patient population.

### 10.1.3.4.1.1.3 Expanded Timed Get-Up-and-Go Test (ETGG)

The ETGG test is a measure of mobility and balance. The ETGG was developed to be an objective tool for assessing at-risk elderly patients for balance problems, mobility skills, and difficulty performing activities of daily living.[6] The test examines a series of different functional mobility tasks, including standing up from a seated position, walking, turning, stopping, and sitting down. Each task is timed individually (sit to stand, reach 2 m mark, reach 8 m mark, reach 8 m mark on return, reach 2 m mark on return, sit down), and the total time to complete the full series of tasks is timed. In clinical studies of young, elderly non-impaired and elderly impaired individuals performing the ETGG, the young and elderly controls performed the ETGG test in <10 seconds. The times in the elderly at-risk groups were all significantly higher than in controls. There are no available norms or previous data for the ETGG in patients with MPS VI.

The ETGG was administered 2 times on separate days, at baseline and at Weeks 6, 12, 24 and 48. Patient assist devices were allowed, but had to be used consistently for each test performed.

One (1) subject was unable to perform the ETGG test at baseline. The results showed that, in general, progressive decreases in time were seen at each visit through Week 48, and at Week 48, 8 of 9 subjects were able to decrease their time to perform the ETGG test from baseline. The change from baseline at Week 48 ranged from -20 to +1 seconds (mean -10), although the clinical relevance of these findings is unknown. The results for the total time to perform the ETGG are summarized in the following table.

6 Wall JC, Bell C, Campbell S, Davis J. The timed get-up-and-go test revisited: Measurement of the component tasks. J Rehab Res Develop 2000;37(1):109-114.

**Table 66. Study ASB-01-04, ETGG Results**

| Subject | Time (seconds) | | | | | Change at Week 48 |
|---|---|---|---|---|---|---|
| | Baseline | Week 6 | Week 12 | Week 24 | Week 48 | |
| 200 | Unable | 56 | 36 | 31 | 36 | * |
| 201 | 31 | 27 | - | 19 | 13 | -18 |
| 202 | 26 | - | 20 | 21 | 20 | -6 |
| 203 | 59 | 56 | 56 | 53 | 39 | -20 |
| 204 | 24 | 26 | 22 | 21 | 19 | -5 |
| 300 | 38 | 46 | 39 | 38 | 39 | +1 |
| 301 | 19 | 17 | 17 | 16 | 13 | -6 |
| 302 | 24 | 32 | 17 | 18 | 17 | -7 |
| 303 | 35 | 18 | 21 | 30 | 22 | -13 |
| 304 | 26 | 19 | 16 | 15 | 13 | -13 |
| **Mean (SD)** | **31** | **35** | **27** | **26** | **23** | **-10** |
| *No baseline result | | | | | | |

### 10.1.3.4.1.1.4 Active and Passive Shoulder Range of Motion (ROM)

The Shoulder Joint Range of Motion (ROM) is an assessment of both active and passive shoulder joint ROM as measured by flexion, extension and rotation using a goniometer. It is noted that in a recent clinical study of α-L-iduronidase in children with MPS I (Hurler, Hurler-Scheie, or Scheie syndrome), changes in shoulder ROM of $\geq 10^{\circ}$ were considered to be clinically significant.[7] Shoulder ROM was performed at baseline and at Weeks 6, 12, 24, and 48, and the mean of 6 shoulder measurements (3 each for right [R] and left [L] shoulder) was used as the result.

The results show limitations in shoulder ROM (flexion, extension and rotation) compared to normal for all subjects at baseline. The changes at Week 48 show considerable variability between subjects and with different measures for the same subject (e.g., a subject may have shown increased flexion, but decreased rotation at Week 48). There was no consistent pattern of improvement or worsening seen over time (data not shown) or in general, and few increases in ROM $\geq 10^{\circ}$ were seen. The active shoulder ROM results at baseline, Week 48 and change from baseline at Week 48 are summarized in the following table.

7 Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Swiedler SJ, Kakkis ED, Braakman T, Chadbourne E, Walton-Bowen K, Cox GF. Enzyme replacement therapy for mucopolysaccharidosis I: A randomized, double-blinded, placebo-controlled multinational study of recombinant human α-L-iduronidase (laronidase). J Pediatr 2004;144:581-588.

**Table 67. Study ASB-01-04, Active Shoulder Flexion, Extension and Lateral Rotation**

| Subject | Parameter | Mean R and L Shoulder ROM | | |
|---|---|---|---|---|
| | | Baseline | Week 48 | Change at Week 48 |
| 200 | Flexion | 97 | 108 | +11 |
| | Extension | 55 | 59 | +4 |
| | Rotation | 56 | 61 | +5 |
| 201 | Flexion | 84 | 97 | +13 |
| | Extension | 59 | 59 | 0 |
| | Rotation | 68 | 73 | +5 |
| 202 | Flexion | 121 | 130 | +9 |
| | Extension | 55 | 59 | +4 |
| | Rotation | 69 | 71 | +2 |
| 203 | Flexion | 105 | 105 | 0 |
| | Extension | 55 | 61 | +6 |
| | Rotation | 55 | 68 | +13 |
| 204 | Flexion | 87 | 92 | +5 |
| | Extension | 62 | 66 | +4 |
| | Rotation | 57 | 52 | -5 |
| 300 | Flexion | 85 | 81 | -4 |
| | Extension | 28 | 37 | +9 |
| | Rotation | 30 | 52 | +22 |
| 301 | Flexion | 121 | 123 | +2 |
| | Extension | 58 | 73 | +15 |
| | Rotation | 76 | 67 | -9 |
| 302 | Flexion | 122 | 123 | +1 |
| | Extension | 51 | 57 | +6 |
| | Rotation | 71 | 68 | -3 |
| 303 | Flexion | 94 | 82 | -12 |
| | Extension | 52 | 55 | +3 |
| | Rotation | 47 | 75 | +28 |
| 304 | Flexion | 109 | 116 | +7 |
| | Extension | 42 | 41 | -1 |
| | Rotation | 63 | 69 | +6 |

### 10.1.3.4.1.1.5 Grip Strength Test

Grip strength was tested using the Marin Vigorimeter bulb. Subjects were seated in chairs, and 3 measurements were obtained for each hand, with a 20-second rest between each measurement. For comparison, 2 studies have been performed that measured grip strength in preschool children (ages 3-6 years [n = 225] or 3-5 years [n = 380] depending on the study) to establish normative data on spherical grip strength. Both studies showed that hand width and grip strength were significantly correlated, and that grip strength increased linearly across all age groups.[8,9] In one study, grip strength for children age 6 years was approximately 36 kilopounds/cm$^2$ (approximately 16 kg/cm$^2$). In the other study, grip strength for children age 5 years was approximately 45 kilopounds/ cm$^2$ (approximately 20 kg/ cm$^2$).

8 Link L, Lukens S, Bush MA. Spherical grip strength in children 3 to 6 years of age. Am J Occup Ther 1995;49(4):318-325

9 Robertson A, Deitz J. A description of grip strength in preschool children. Am J Occup Ther 1987;42(10):647-652.

Grip strength was tested at baseline and at Weeks 6, 12, 24 and 48. The testing for grip strength was inconsistent for 4 of 10 subjects, as different dynamometers and bulbs were used across assessment, and only 6 of 10 patients used the same device at all assessments. The use of different equipment over the duration of the study may have affected the results.

The results showed a wide range of grip strengths at baseline (0/unable to perform to 33 kg; mean 8 kg), with 8 of 10 patients having a grip strength below the expected norms for 5-6 year old children. At Week 48 (range 0 to 21 kg; mean 9 kg), 9 of 10 subjects had grip strengths below expected norms. There was no indication of consistent increases in grip strength over the duration of the study, with considerable variability in grip strength for some subjects from visit to visit. There was a wide range of change in grip strengths (-22 kg to +10 kg) at Week 48, with 7 of 10 subjects having any increase in grip strength (range +1 to +10 kg), 1 subject having no change, and 2 subjects having a decrease (-1 and -22 kg) in grip strength. The clinical relevance of these findings is unknown, and it is additionally noted that there is no accepted cutpoint for an increase in grip strength that is considered clinically significant.

### 10.1.3.4.1.1.6 Pinch Strength

Pinch strength was tested using the B&L mechanical pinch gauge. Three measurements of maximum key pinch strength were obtained at each timepoint. For comparison, at least 1 study has been performed in adults (including normals and subjects with upper extremity pathology) to establish normative data on pinch strength scores (n = 40; age range 19-80 years, mean age = 32 years). This study showed average pinch strength scores of approximately 9 kg.[10]

Pinch strength was assessed at baseline and at Week 6, 12, 24 and 48. As with grip strength (above), pinch gauge sizes were not consistently used for all assessments for each patient, with only 5 of 10 patients using the same size gauge for all assessments. The use of different equipment over the duration of the study may have affected the results.

The results showed a wide range of pinch strengths at baseline (1.0 to 6.6 kg; mean 3.5 kg) with all subjects having a pinch strength below expected norms (for adults). At Week 48, there were wide ranges in pinch strength (1.6 to 8.1 kg; mean 4.2 kg), all of which were below expected norms. In general, subjects showed a progressive increase in pinch strength through Week 48. Eight of 10 subjects showed any increase in pinch strength from baseline at Week 48, and 2 subjects showed a decrease. Change in pinch strength from baseline at Week 48 ranged from -0.2 to +1.5 kg (mean 0.8 kg). The clinical relevance of these findings is unknown.

### 10.1.3.4.1.1.7 Pain and Joint Stiffness

The Childhood Pain and Joint Stiffness Questionnaire and the Adult Pain and Joint Questionnaire were used to assess pain and joint stiffness (both questionnaires ask similar questions). The Childhood Pain and Joint Stiffness Questionnaire was completed by a parent for subjects who were 18 years of age and younger, and the same parent completed the questionnaire at each visit to avoid inconsistencies. The Adult Pain and Joint Stiffness Questionnaire was completed by the subject for patients 19 years of age or older. The pain score is subjectively reported on a scale from zero (no pain) to 100 (very severe pain), and the stiffness score is subjectively reported on a scale from zero (no joint stiffness and limit in ability) to 100 (severe joint stiffness and severely limited in activity). Pain and joint stiffness are assessed in 2 ways in the questionnaires: 1) scores for pain and joint stiffness are rated during the past week; and 2)

10 MacDermid JC, Evenhuis W, Louzon M. Inter-instrument reliability of pinch strength scores. J Hand Ther 2001;14:36-42.

scores for pain and joint stiffness are rated compared to baseline. Pain and joint stiffness were assessed at baseline and at Weeks 6, 12, 24 and 48.

Baseline assessments were not performed for 2 subjects (Subjects 203 and 204). For the 8 subjects with baseline results, baseline pain scores ranged from 0 to 60 (mean 36), and stiffness scores ranged from 40 to 100 (mean 64). In general, pain and stiffness scores tended to decrease at each visit from baseline through Week 48. At Week 48 (n = 8), pain scores ranged from 0 to 80 (mean 17), and stiffness scores ranged from 0 to 55 (mean 23). All subjects with a baseline score (n = 8) had at least some decrease in stiffness at Week 48, and 6 of 8 subjects had at least some decrease in pain at Week 48 (1 subject had no change and 1 subject had an increase in pain score) . The change in scores from baseline at Week 48 for pain ranged from -50 to +30 (mean -19) and for stiffness ranged from -15 to -70 (mean -41).

These results should be interpreted with caution as the pain and stiffness scores are subjective measures, and this was an uncontrolled, open-label study.

### 10.1.3.4.1.1.8 MPS VI Quality of Life (QoL) Profile

The MPS VI QoL profile measured the degree of difficulty and time required to perform 4 tasks, including: putting on shoes, touching the top of the head with both hands, putting on and taking off a sweatshirt, and picking up 10 coins from a table top and putting them into a cup. Subjects were rated on each activity using the following scale: 1) without any difficulty; 2) with some difficulty; and 3) unable to do. For the first 3 tasks, many of the subjects were unable to perform these tasks at baseline or at any of the assessment points, and there were few changes in difficulty or time required to perform the tasks over the duration of the study. All subjects, however, were able to perform the coin pick-up test, and all subjects were able to place all 10 coins in a cup within the 3-minute time limit at each assessment. Thus, the results for the Coin Pickup test only are summarized below.

At baseline, coin pickup times ranged from 15 to 80 seconds (mean 38 seconds) and at Week 48, times ranged from 10 to 40 seconds (mean 21 seconds). All subjects improved their time from baseline to Week 48, with a change at Week 48 ranging from -2 to -40 seconds (mean -17). The clinical relevance of these results and of this test as a measure of efficacy for MPS VI is unknown.

### 10.1.3.4.1.1.9 Urinary GAGs Levels

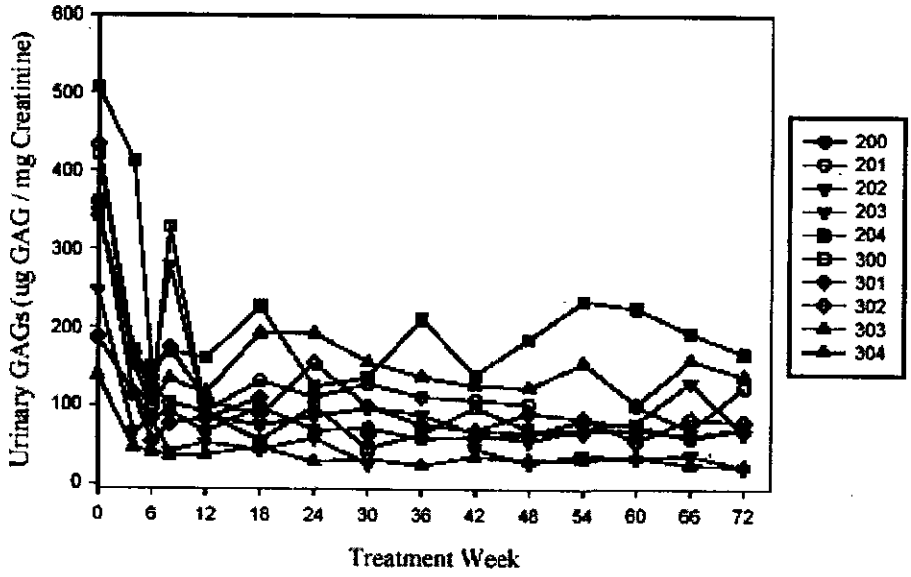
The urinary GAGs level was measured (for each subject) 3 times at baseline, once at Weeks 1, 4, 6, 8, 12, 18, and 24, and every 6 weeks thereafter through Week 72. The analysis was performed on the first morning voided urine specimen. At baseline, urinary GAGs levels ranged from 138.4 to 518.5 μg/mg Cr (ranges for normal subjects from 50.5 μg/mg Cr in 4 to 6 year olds to 11.1 μg/mg Cr in >18 year olds). Urinary GAGs levels decreased by Week 6 in all subjects, and remained decreased throughout the 72-week treatment period. The results are summarized in the following table.

**Table 68. Study ASB-01-04, Urinary GAGs Levels, Baseline through Week 72**

| Subject (age) | Baseline (µg/mg Cr) | Treatment Week (+2 weeks) (µg/mg Cr) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 4 | 6 | 8 | 12 | 18 | 24 | 36 | 48 | 60 | 72 |
| 200 (17) | 361 | 315 | 114 | 85 | 92 | 67 | 99 | 69 | 59 | 65 | 75 | 71 |
| 201 (8) | 342 | 575 | 160 | 106 | 104 | 93 | 132 | 112 | 112 | 103 | 100 | 124 |
| 202 (16) | 247 | 271 | 66 | 81 | 42 | 53 | 44 | 59 | ND | 27 | 33 | 22 |
| 203 (14) | 347 | 440 | 174 | 122 | 280 | 88 | 75 | 87 | 90 | 55 | 80 | 65 |
| 204 (6) | 519 | 550 | 413 | 151 | 170 | 160 | 227 | 125 | 221 | 186 | 225 | 167 |
| 300 (21) | 422 | 513 | 153 | 100 | 328 | 90 | 55 | 100 | 65 | 70 | 68 | 73 |
| 301 (9) | 187 | 186 | 115 | 54 | 77 | 84 | 94 | ND | ND | 65 | 70 | 70 |
| 302 (6) | 434 | 300 | 167 | 136 | 175 | 106 | 89 | 155 | 76 | 91 | 55 | 80 |
| 303 (8) | 361 | 341 | 117 | 106 | ND | 117 | 88 | 193 | 137 | 123 | 102 | 19 |
| 304 (16) | 138 | 167 | 46 | 41 | 36 | 38 | 47 | 29 | 24 | 31 | 34 | 23 |
| **Mean** | **336** | **366** | **152** | **98** | **149** | **90** | **95** | **103** | **98** | **82** | **84** | **83** |
| **Median** | **354** | **328** | **135** | **103** | **104** | **89** | **88** | **100** | **83** | **68** | **73** | **72** |

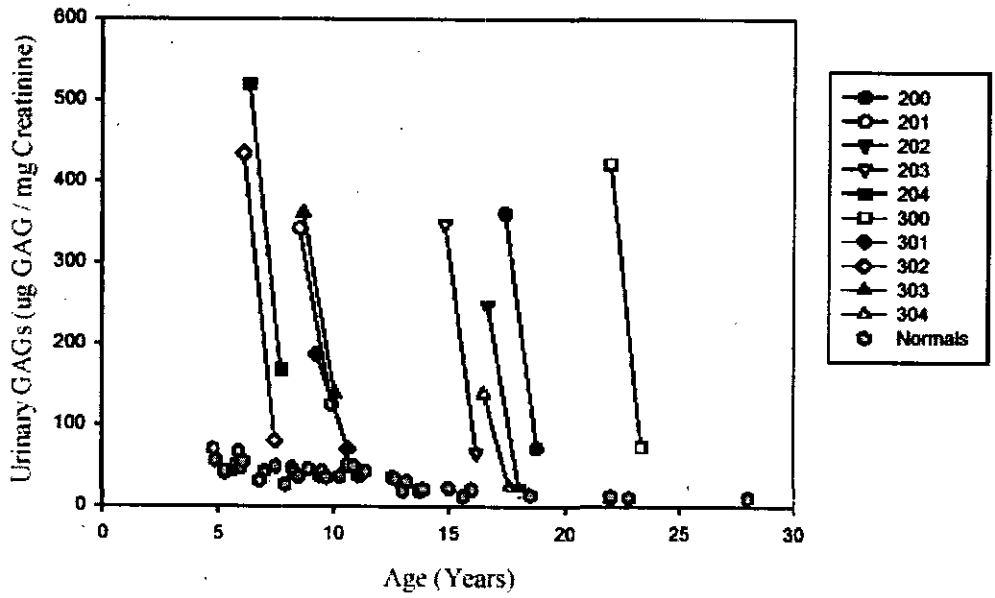
The results are also represented graphically in the following figure (electronically copied and reproduced from the sponsor's submission):

**Figure 16. Study ASB-01-04, Urinary GAGs Levels at Baseline over 72 Weeks of Treatment**




Additionally, the sponsor plotted each subject's baseline and Week 72 urinary GAGs levels compared to age-matched normal values. All subjects' urinary GAGs levels approached age-matched normal values at Week 72, and 2 subjects (Subjects 202 and 304) had urinary GAGs levels within normal ranges for age at Week 72. The results are depicted graphically in the following figure (electronically copied and reproduced from the sponsor's submission):

**Figure 17. Study ASB-01-04, Urinary GAGs Levels at Baseline and Week 72 Compared to Normal Values**




These results are consistent with a pharmacodynamic effect of the enzyme, but do not imply any clinical benefit of treatment.

**10.1.3.4.1.2 Secondary Efficacy Endpoints**

The secondary efficacy endpoints were change from baseline in the following measures:

- ActiTrac Physical Activity Monitoring
- PFT's
- Electrocardiogram (ECG) and Echocardiogram Results
- Visual Examination
- Oxygenation during Sleep (all patients) and Sleep Study (Australia only)
- Linear Growth
- Abdominal CT Scans (liver and spleen size)
- Bone mineral Densitometry (US only)

*ActiTrac Physical Activity Monitoring*

Physical activity was recorded with the FDA-approved ActiTrac (a device worn attached to a belt that records physical motion in 2 planes). Subjects were to wear the ActiTrac for 5 continuous days at each time point (baseline and at Week 6, 12, 24 and 48). Data collected by the ActiTrac was then downloaded to a computer for analysis.

The data obtained for this endpoint were unreliable (personal communication with the sponsor). All subjects did not consistently wear the devices for the full 5 days at all assessments and the readings on the device could easily be changed by such things as shaking the monitor (shaking would be recorded as activity).Thus, no further analysis of this endpoint will be undertaken.

*Pulmonary Function Tests (PFT's)*

Pulmonary function was evaluated by determining Forced Vital Capacity (FVC), Forced Expiratory Time in seconds (FET), and Forced Expiratory Volume for one second (FEV1) in accordance with American Thoracic Society (ATS) standards. The test was conducted 2 times on separate days at baseline and at Weeks 24, 48 and 72. In the Survey Study (Study ASB-03-05 submitted with this BLA), MPS VI subjects had low lung volumes based on FVC due to the underlying skeletal disease of MPS VI, e.g., short stature, size of the thorax, and restrictive disease due to the dysplastic changes in the ribcage. There is no standard curve that reflects the height and dysplastic changes seen for patients with MPS VI, thus, calculation of a percent predicted FVC was felt (by the sponsor) to be meaningless and was not done. In addition, changes in PFT measures must be interpreted with consideration to other factors that influence lung volumes, such as change in height and decreases in the liver and spleen volumes that occurred for most patients in the study.

The results showed that in general, no consistent changes in FET, FVC or FEV1 from baseline were seen over the 72 weeks of the study. For FVC, 4 subjects (Subjects 201, 203, 204 and 303) had increases in FVC $\geq$ 10% from baseline at Week 72, 1 subject (Subject 301) had a $\geq$ 10% decrease in FVC (-0.28 L), and the remaining 5 subjects had little change from baseline. For the subjects with the $\geq$ 10% increases in FVC, the magnitude of these changes was small (range 0.04 to 0.11 L). All 4 subjects had increases in height (2 to 7.5 cm), and 3 of the 4 had notable decreases in liver and spleen volume during the study. The subject with the largest increase in FVC (Subject 303; 0.11 L) also had a notable improvement in asthma and was able to discontinue steroids. For $FEV_1$, 3 subjects had an increase in $FEV_1 \geq 10\%$ (Subjects 200, 203 and 303), and 7 subjects had little changes from baseline at Week 72. For the 3 subjects with an increase in $FEV_1 \geq 10\%$, the magnitude of the changes was small (0.03 to 0.10 L), 2 of the 3 subjects had increases in height (2 cm each), and the subject with the largest increase was the subject with the notable improvement in asthma (Subject 303). For FET, there was considerable variability in change from baseline at Week 72 across the 10 subjects, considerable variability in results for each subject by week tested, and no consistent or progressive pattern of improvement was seen over the course of the study.

Thus, overall for the PFT's results, no notable, clinically meaningful change in any parameter could be discerned. The changes from baseline over the 72 weeks of treatment for FVC, FEV1, and FET are summarized in the following table:

**Table 69. Study ASB-01-04, PFT's**

| Subject | Measure | Baseline | Week 48 | Week 72 | Change from Baseline | Comments |
|---|---|---|---|---|---|---|
| 200 | FET (sec) | 5.12 | 6.21 | 5.04 | -0.08 | No change in height Age 17 |
| | FVC (L) | 0.47 | 0.48 | 0.44 | -0.03 | |
| | $FEV_1$ (L) | 0.30 | 0.36 | 0.33 | +0.03 | |
| 201 | FET (sec) | 3.34 | 5.09 | 4.82 | +1.48 | Height increase 7.5 cm Age 8 |
| | FVC (L) | 0.52 | 0.60 | 0.57 | +0.05 | |
| | $FEV_1$ (L) | 0.38 | 0.43 | 0.48 | +0.10 | |
| 202 | FET (sec) | 5.14 | 6.92 | 5.47 | +0.33 | No change in height Age 16. Reduction in liver and spleen size |
| | FVC (L) | 0.75 | 0.92 | 0.83 | +0.08 | |
| | $FEV_1$ (L) | 0.57 | 0.73 | 0.72 | +0.15 | |
| 203 | FET (sec) | 1.95 | 4.52 | 3.34 | +1.39 | Increase in height 2.4 cm Age 14. Reduction in liver and spleen size |
| | FVC (L) | 0.28 | 0.38 | 0.32 | +0.04 | |
| | $FEV_1$ (L) | 0.25 | 0.34 | 0.30 | +0.05 | |
| 204 | FET (sec) | 3.47 | 5.39 | 8.53 | +5.06 | Height increase 5.3 cm Age 6 |
| | FVC (L) | 0.52 | 0.50 | 0.60 | +0.08 | |
| | $FEV_1$ (L) | 0.45 | 0.40 | 0.42 | -0.03 | |
| 300 | FET (sec) | 1.15 | 1.53 | 1.83 | +0.68 | Height increase 2.2 cm Age 21 |
| | FVC (L) | 0.37 | 0.37 | 0.38 | +0.01 | |
| | $FEV_1$ (L) | 0.37 | 0.35 | 0.37 | 0 | |
| 301 | FET (sec) | 2.87 | 2.83 | 3.47 | +0.60 | Height increase 7.5 cm Age 9 |
| | FVC (L) | 1.35 | 1.55 | 1.07 | -0.28 | |
| | $FEV_1$ (L) | 1.71 | 1.38 | 1.60 | -0.11 | |
| 302 | FET (sec) | 2.05 | 2.95 | 1.85 | -0.20 | Height increase 5.7 cm Age 6 |
| | FVC (L) | 0.81 | 0.83 | 0.86 | +0.05 | |
| | $FEV_1$ (L) | 0.79 | 0.79 | 0.83 | +0.04 | |
| 303 | FET (sec) | 1.16 | 2.25 | 1.06 | -0.10 | Height increase 2 cm Age 8. Improvement in asthma (steroids stopped). Reduction in spleen and liver sizes |
| | FVC (L) | 0.16 | 0.31 | 0.27 | +0.11 | |
| | $FEV_1$ (L) | 0.16 | 0.31 | 0.26 | +0.10 | |
| 304 | FET (sec) | 1.86 | 3.87 | 3.76 | +1.90 | Height increase 1.5 cm Age 16 |
| | FVC (L) | 0.83 | 0.83 | 0.87 | +0.04 | |
| | $FEV_1$ (L) | 0.81 | 0.76 | 0.79 | -0.02 | |

*Electrocardiogram and Echocardiogram Results*

No clinically relevant, noteworthy or significant changes were seen in any subject in the ECG or echocardiogram results from baseline through Week 48.

*Visual Examination*

Visual examination (fundoscopy) of the retina and optic nerve, a slit lamp examination of the cornea, measures of intraocular pressure, and best corrected visual acuity were performed at baseline and Week 48. No clinically significant changes were seen in the fundoscopic and slit lamp evaluations in any subject. Four (4) subjects (Subjects 201, 204, 300 and 304) had improvements in visual acuity of $\geq 2$

lines in at least 1 eye. One subject (Subject 304) had improved acuity in the right eye (from 20/60 to 20/30), but worsened in the left (from 20/80 to 20/200).

Six subjects (Subjects 200, 202, 300, 302, 303 and 304) had elevated intraocular pressure at baseline (≥ 20 mmHg). At Week 48, 4 of these subjects had decreases in pressure, 3 of which had decreases to <20 mmHg; however, the decreases in pressure were felt to be secondary to changes in medications and better compliance with prescribed medications, and not due to study drug. One subject (Subject 300) had increases in pressure in both eyes at Week 48, and Subject 304 had no change. One subject (Subject 203), had pressure <20 mmHg at baseline, and an increase in pressure to 21 mmHg in both eyes at Week 48. Thus, overall, there were no clinically meaningful changes in the visual exam that could be attributed to study drug.

*Oxygenation During Sleep*

Continuous oxygen saturation during sleep was performed at home with a pulse oximeter, using the patient's standard respiratory support, e.g., oxygen, CPAP, etc. The mean saturation, lowest saturation, number and duration of desaturations, and percent of time that oxygen saturation was below 90% and 80% were recorded. The test was performed twice on separate days at baseline and at Weeks 12, 24 and 48. The results showed little change in the average or lowest $O_2$ saturation over the course of the study, but the sponsor noted that the 2 subjects with long periods of $O_2 < 90$ % showed decreases in the total number of desaturations between baseline and Week 48.

The 5 subjects enrolled into the primary site in Australia had sleep studies performed at baseline, Week 24 and Week 48. Three of these subjects (Subjects 301, 303 and 304) were using CPAP, BiPAP or VPAP, respectively, at baseline. In the remaining 2 subjects (Subjects 300 and 302), Subject 302 had increases in obstructive apnea and hypopnea indices from baseline to Week 48. Subject 300 had little change from baseline to Week 48 in these indices, but had increases in total sleep time, with fewer arousals per hour of sleep, and decreases in total central apnea events, and in the percent of total sleep time with tcCO2 > 50 mm. No conclusions as to the study drug's effects on sleep studies can be drawn from the results of only 2 subjects.

*Linear Growth*

Standing height was measured at baseline and Weeks 48 and 72. Two subjects had no height determination at Week 72 (Subject 200 [age 17] and Subject 202 [age 16]). In the remaining 8 of 10 subjects with a height determination at baseline and Week 72, all subjects had an increase in height ranging from 1 to 8 cm.

When evaluated by age, the change in height was greatest in 4 of the 5 prepubertal subjects (ages 6-9 years), with change in height from baseline at Week 72 ranging from 2 to 8 cm (mean 5 cm), and smallest in the 3 oldest subjects (ages 14-21 years) with baseline and Week 72 data (range 1-3 cm, mean 2 cm). The results for height arranged by age from low to high are summarized in the following table

**Table 70. Study ASB-01-04, Height Arranged by Age (Low to High)**

| Subject | Age at Baseline (yrs) | Height (cm) | | | Change at Week 72 (cm) |
|---|---|---|---|---|---|
| | | Baseline | Week 48 | Week 72 | |
| 204 | 6 | 87 | 91 | 92 | 5 |
| 302 | 6 | 100 | 105 | 105 | 5 |
| 201 | 8 | 93 | 100 | 101 | 8 |
| 303 | 8 | 85 | 86 | 87 | 2 |
| 301 | 9 | 122 | 127 | 129 | 7 |
| 203 | 14 | 107 | 109 | 109 | 2 |
| 202 | 16 | 120 | 121 | Not done | - |
| 304 | 16 | 125 | 126 | 126 | 1 |
| 200 | 17 | 96 | 96 | Not done | - |
| 300 | 21 | 102 | 105 | 105 | 3 |

No information regarding the subjects' growth velocity or growth curves prior to enrollment in the study were provided, so it is not possible to determine if study drug had an effect on growth or if there was a change from each subject's growth pattern.

*Abdominal CT Scans*

A CT scan of the abdomen to assess bone density (US only) and liver and spleen size was conducted at baseline and Week 48. On physical examination (PE), all 10 subjects had evidence of hepatomegaly and 4 subjects had evidence of splenomegaly at baseline. When liver and spleen weights were calculated by CT scan, all subjects had spleen weights above the 95% CI for age at baseline, and 5 subjects (Subjects 201, 200, 202 303 and 304) had liver weights as a percent of body weight > 95% CI for age. All subjects but one (Subject 301) had decreases in liver volume at Week 48, and all subjects except 2 (Subject 301 and 304) had decreases in spleen volume at Week 48. For the 10 subjects with spleen volume as a percent of body weight > 95 % CI at baseline, 3 subjects (200, 202, and 203) had spleen weight as a percent of body weight < 95 % CI at Week 48. For the 5 subjects with liver weight as a percent of body weight > 95 % CI at baseline, 3 had liver weight as a percent of body weight < 95 % CI at Week 48. These decreases in liver and spleen size are summarized in the following table.

**Table 71. Study ASB-01-04, Liver and Spleen Size**

| Subject (age, gender) | Organ | Organ size ($cm^3$) | | Organ Wt as % of Body Wt | |
|---|---|---|---|---|---|
| | | Baseline | Week 48 | Baseline | Week 48 |
| 200 (17, F) | Liver | 584 | 547 | 2.9 | 2.5 |
| | Spleen | 102 | 96 | 0.5 | 0.4 |
| 201 (8, M) | Liver | 747 | 730 | 3.7 | 3.1 |
| | Spleen | 136 | 124 | 0.7 | 0.5 |
| 202 (16, F) | Liver | 794 | 741 | 2.4 | 2.3 |
| | Spleen | 151 | 109 | 0.5 | 0.3 |
| 203 (14, F) | Liver | 711 | 650 | 2.4 | 2.1 |
| | Spleen | 152 | 127 | 0.5 | 0.4 |
| 204 (6, F) | Liver | 471 | 465 | 3.1 | 3.0 |
| | Spleen | 89 | 83 | 0.6 | 0.5 |
| 300 (21, F) | Liver | 750 | 634 | 3.6 | 2.9 |
| | Spleen | 199 | 166 | 1.0 | 0.8 |
| 301 (9, M) | Liver | 791 | 998 | 2.5 | 2.7 |
| | Spleen | 183 | 219 | 0.6 | 0.6 |
| 302 (6, M) | Liver | 561 | 593 | 3.0 | 2.6 |
| | Spleen | 104 | 102 | 0.6 | 0.5 |
| 303 (8, F) | Liver | 600 | 565 | 4.0 | 3.5 |
| | Spleen | 150 | 82 | 1.0 | 0.5 |
| 304 (16, F) | Liver | 808 | 785 | 2.8 | 2.4 |
| | Spleen | 202 | 216 | 0.7 | 0.7 |

Liver weight as % of body weight upper 95% CI:
Females: 5-12 years = 3.22; 13-17 years = 2.73; ≥18 years = 2.88
Males: 5-12 years = 3.48; 13-17 years = 2.65; ≥18 years = 2.57
Spleen weight as % of body weight upper 95% CI:
Females: 5-12 years = 0.351; 13-17 years = 0.404; ≥18 years = 0.328
Males: 5-12 years = 0.402; 13-17 years = 0.350; ≥18 years = 0.309

*Bone Mineral Density*

CT scans to assess bone density (T- and L-spine) were performed at baseline and Week 48 for the 5 subjects enrolled at the primary center in the US only. There were no clinically meaningful changes in bone densitometry from baseline at Week 48 in any subject.

*Pharmacokinetic Endpoints*

PK samples were obtained at Weeks 1, 2, 12 and 24. Samples were obtained at baseline (30 minutes prior to infusion), then at 30, 90 and 180 minutes after the start of the infusion, and post-infusion at 5, 10, 20, 30, 45 and 90 minutes after the end of the infusion.

The results showed that the $AUC_{0-t}$ increased from Week 1 to Week 2, then remained relatively constant through Week 24. The t ½ ranged from 15 to 19 minutes and did not change appreciably by week through Week 24. The PK results are summarized in the following table:

**Table 72. Study ASB-01-04, PK Parameters for Galsulfase**

| Parameter | Week 1 | Week 2 | Week 12 | Week 24 |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 757 ± 270 | 1176 ± 416 | 1313 ± 546 | 1701 ± 659 |
| $T_{max}$ (min) | 180 | 181 | 180 | 222 |
| $AUC_{0-t}$ (min•ng/mL) | 135,043 ± 42,479 | 200,730 ± 72,793 | 204,049 ± 87,581 | 254,757 ± 88,010 |
| $AUC_{\infty}$ (min•ng/mL) | 135,659± 41,550 | 207,810 ± 74,588 | 250,921 ± 87,989 | 274,570 ± 94,548 |
| CL (mL/min/kg) | 8.0 ± 2.7 | 5.5 ± 2.3 | 6.7 ± 5.9 | 4.0 ± 1.2 |
| $V_z$ (mL/kg) | 233 ± 223 | 137 ± 94.4 | 163 ± 197 | 94.4 ± 50.7 |
| $V_{ss}$ (mL/kg) | 363 ± 148 | 270 ± 107 | 501 ± 665 | 221 ± 60.7 |
| $t_{1/2}$ (min) | 19 ± 17 | 16.5 ± 6.3 | 15.3 ± 10.9 | 17.7 ± 9.5 |
| MRT (min) | 45.3 ± 8.2 | 49.3 ± 4.0 | 62.6 ± 19.9 | 57.0 ± 10.9 |

*Safety*

Safety was evaluated by serial physical examinations, vital signs (VS), anti-galsulfase antibody levels, measures of complement activations, clinical laboratory evaluations (chemistry and hematology panels), ECG and recording of AEs.

10.1.3.4.1.2.1 Exposure

There were no study drug discontinuations during the 72 weeks of the study, and subjects received a mean of 72 infusions of galsulfase 1.0 mg/kg over the 72-week study period, ranging from 71 to 73 infusions. One subject missed 2 infusions due to drug shipment difficulties and 1 subject missed 1 infusion due to a febrile illness prior to the infusion.

10.1.3.4.1.2.2 Adverse Events

All Adverse Events

Adverse Events (AEs) experienced by the subject from the time of signing of the Informed Consent through the Week 72 infusion were recorded. All AEs were coded and listed (by the sponsor) by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. There were a total of 377 AEs recorded during the study, and all 10 subjects experienced at least 1 AE at sometime during the study. The sponsor's AE summary was reviewed by this Reviewer, and duplicate terms were added together (e.g., URI and viral URI were added together). By this review, there were a total of 96 different AE terms reported. All 10 subjects experienced an infection at some time during the study, and the most commonly reported AEs were: URI/ rhinitis (9 patients), arthralgia (8), and headache (6). Other frequently reported AEs included GI symptoms (diarrhea [5], vomiting [5], abdominal pain [4]), ear-related symptoms (otitis [5], otorrhea [5], and ear pain [4]), fever/rigors (5), infusion site pain (5), and pneumonia (4). In general, the types of AEs reported tended to reflect the underlying disease (such as sleep apnea, infections and ear-related symptoms); however, as there was no control group, it is not possible to discern which AEs may have had an increased incidence with study drug use. All AEs reported during the study are summarized in the following table.

**Table 73. Study ASB-01-04, All AEs**

| Event/Term | Incidence (%) | Event/Term | Incidence (%) |
|---|---|---|---|
| Infection | 10 (100) | Bronchitis | 1 (10) |
| URI/Rhinitis | 9 (90) | Carpal tunnel | 1 (10) |
| Arthralgia | 8 (80) | Cerumen impaction | 1 (10) |
| Headache | 6 (60) | Chest wall pain | 1 (10) |
| Diarrhea | 5 (50) | Complement decreased | 1 (10) |
| Fever/Rigors | 5 (50) | Conduction disturbance | 1 (10) |
| Infusion site pain | 5 (50) | Congestive heart failure | 1 (10) |
| Otitis | 5 (50) | Corneal opacity | 1 (10) |
| Otorrhea | 5 (50) | Ear congestion | 1 (10) |
| Poor venous access | 5 (50) | Ear hemorrhage | 1 (10) |
| Vomiting | 5 (50) | Elevated INR | 1 (10) |
| Abdominal pain | 4 (40) | Eye redness | 1 (10) |
| Burn | 4 (40) | Gingival bleeding | 1 (10) |
| Ear pain | 4 (40) | Groin pain | 1 (10) |
| Pneumonia | 4 (40) | Motion sickness | 1 (10) |
| Rash | 4 (40) | Head injury | 1 (10) |
| Sleep apnea | 4 (40) | Hernia pain | 1 (10) |
| Contusion | 3 (30) | Hydrocephalus | 1 (10) |
| Cough | 3 (30) | Hypokalemia | 1 (10) |
| Ear effusion | 3 (30) | Increased intraocular pressure | 1 (10) |
| Extremity pain | 3 (30) | Joint deformity | 1 (10) |
| Nausea | 3 (30) | Joint injury | 1 (10) |
| Pain back | 3 (30) | Joint sprain | 1 (10) |
| Pleuritic chest pain | 3 (30) | Joint stiffness | 1 (10) |
| Visual acuity reduced | 3 (30) | Keratoconjuctivitis sicca | 1 (10) |
| Asthma/Wheeze | 2 (20) | Laceration | 1 (10) |
| Confusion/Agitation/Anxiety | 2 (20) | Lung disorder | 1 (10) |
| Conjunctivitis | 2 (20) | Mouth ulceration | 1 (10) |
| Constipation | 2 (20) | Muscle cramps | 1 (10) |
| Dyspnea | 2 (20) | Osteonecrosis | 1 (10) |
| Excoriation | 2 (20) | Pallor | 1 (10) |
| Eyelid edema | 2 (20) | Photophobia | 1 (10) |
| Eye pain | 2 (20) | Pneumonitis | 1 (10) |
| Gastroenteritis | 2 (20) | Pulmonary hypertension | 1 (10) |
| Hearing impairment | 2 (20) | Rales | 1 (10) |
| Herpes simplex | 2 (20) | Sneezing | 1 (10) |
| Infusion site bruising | 2 (20) | Spinal stenosis | 1 (10) |
| Infusion site reaction/Erythema | 2 (20) | Splenomegaly | 1 (10) |
| Laryngitis/Hoarseness | 2 (20) | Subconjunctival hemorrhage | 1 (10) |
| Myalgia | 2 (20) | Syncope | 1 (10) |
| Neck pain | 2 (20) | Tooth fracture | 1 (10) |
| Pharyngitis | 2 (20) | Tooth impacted | 1 (10) |
| Pruritus | 2 (20) | Tooth loss | 1 (10) |
| Albumin decreased | 1 (10) | Umbilical hernia | 1 (10) |
| Anal fissure | 1 (10) | Urinary incontinence | 1 (10) |
| Anorexia | 1 (10) | Valve disorder | 1 (10) |
| Arthropod sting | 1 (10) | Vertigo/Dizziness | 1 (10) |
| Asthenia/Fatigue | 1 (10) | Viral illness | 1 (10) |

Of the AEs listed above, 7 AEs in 7 subjects were considered by the Investigator to have been severe. No severe AE term was reported twice, one severe AE (abdominal pain) was considered as at least possibly related to study medication by the Investigator, and one severe AE was also classified as serious (pneumonia). All subjects recovered from the severe AEs by the end of the study except 1 (Subject 203), whose sleep apnea was reported as continuing. The severe AEs reported during the study are summarized in the following table.

**Table 74. Study ASB-01-04, Severe Adverse Events**

| Subject | SOC | Preferred Term | Relatedness | Outcome | Serious |
|---|---|---|---|---|---|
| 200 | Infections and infestations | URI | Unrelated | Recovered | N |
| 201 | Nervous system disorders | Headache | Unrelated | Recovered | N |
| 202 | Eye disorders | Corneal opacity | Unrelated | Recovered | N |
| 203 | Nervous system disorders | Sleep apnea syndrome | Unrelated | Continuing | N |
| 204 | Infections and infestations | Otitis media | Unrelated | Recovered | N |
| 300 | Infections and infestations | Pneumonia | Unrelated | Recovered | Y |
| 304 | Gastrointestinal disorders | Abdominal pain | Possibly | Recovered | N |

## Serious Adverse Events (SAEs)

There were 8 Serious AEs (SAEs) experienced by 4 subjects reported during the study, including pneumonia (2), sleep apnea (2), dyspnea (1), INR abnormal (1), asthma (1) and pain in extremity (1). There were no deaths, and no patient discontinued study drug due to an SAE (or due to an AE). Only asthma was considered by the Investigator to be at least possibly related to study medication. All subjects recovered from the SAEs by the end of the study except 1 patient (Patient 301), whose sleep apnea was reported as continuing. The SAEs reported during the study are summarized in the following table

**Table 75. Study ASB-01-04, Serious Adverse Events**

| Subject | SOC | Preferred Term | Relatedness | Outcome |
|---|---|---|---|---|
| 202 | Infections and Infestations | Pneumonia | Unrelated | Recovered |
| 300 | Infections and infestations | Pneumonia | Unrelated | Recovered |
| 300 | Respiratory, thoracic and mediastinal disorders | Dyspnea | Unrelated | Recovered |
| 300 | Investigations | INR abnormal | Unrelated | Recovered |
| 300 | Nervous system disorders | Sleep apnea | Unrelated | Continuing |
| 301 | Nervous system disorders | Sleep apnea | Unrelated | Recovered |
| 303 | Respiratory thoracic and mediastinal disorders | Asthma | Possibly | Recovered |
| 303 | Musculoskeletal and connective tissue disorders | Pain in extremity | Unrelated | Recovered |

## Infusion-Associated Reactions (IARs)

AEs that occurred during infusion and were judged to be at least possibly related to study drug were considered infusion-associated reactions (IARs). IARs were considered as potential symptoms or signs of an anaphylactoid reaction to galsulfase if they met the following criteria: they recurred during multiple infusions, they improved with a decrease in study drug infusion rate or interruption, or they improved with additional antihistamine or steroid treatment.

Six subjects had a total of 54 AEs that occurred during study drug infusion. All reported AEs that occurred during study drug infusion are summarized in the following table (Note: an individual subject may have experienced more than 1 episode of a listed AE. For example, all 18 instances of rash occurred in Subject 302 and in no other subject).

**Table 76. All Reported AEs during Infusion**

| AE Preferred Term | # of Occurrences |
|---|---|
| Rash | 18 |
| Pyrexia | 11 |
| Vomiting | 3 |
| Rigors | 3 |
| Headache | 3 |
| Urticaria | 3 |
| Hypotension | 2 |
| Nausea | 1 |
| Catheter site pain | 1 |
| Chest pain | 1 |
| Infusion site pain | 1 |
| Prostration | 1 |
| Respiratory tract infection | 1 |
| Anorexia | 1 |
| Pain in extremity | 1 |
| Dystonia | 1 |
| Crackles lung | 1 |
| Dyspnea | 1 |

Of the 54 AEs occurring during infusion, all were rated as mild or moderate by the Investigator, except for 3 which were rated severe (rash [2] and urticaria [1]). The 3 severe AEs were all experienced by Subject 302, and were felt to be related to study drug by the Investigator.

Two (2) subjects experienced recurrent AEs during infusion that were considered probably anaphylactoid reactions (by the definition for IAR above). These included:

- Subject 201 experienced 4 episodes of chills, fever and urticaria with study drug infusion between Week 41 and 58 (but never on consecutive weeks), and on 1 occasion additionally experienced prostration. These episodes responded to interruption/slowing of the infusion, and treatment with ibuprofen, paracetamol and antihistamines. On one occasion, hydrocortisone was administered.
- Subject 302 experienced reactions during all infusions but 2 between Weeks 35 and 53. AEs included hypotension, urticaria, vomiting, and rash. The reactions responded to interruption/slowing of the infusion, and treatment with antihistamines. On one occasion, methylprednisolone was given.

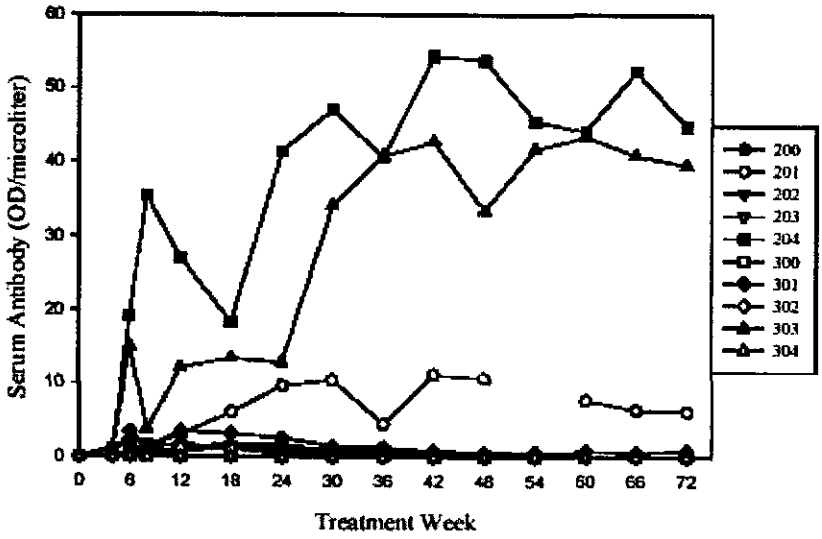
In all cases, the complete dose of study medication was able to be administered

### 10.1.3.4.1.2.3 Anti-Galsulfase Antibodies

All subjects except Subject 304 developed a measurable antibody response (lower limit of quantitation = —)D/μL). However, only 3 subjects (Subject 201, 204 and 303) developed an antibody level 3.5 OD/μL. The 3 subjects with the highest antibody levels did not experience any anaphylactoid reactions; however these 3 subjects also had the highest urinary GAGs levels throughout most of the study period, implying some neutralization of study drug pharmacodynamic effect by antibody formation. The 2 subjects with the highest antibody responses (Subjects 204 and 303) also had evidence of mild complement decreases, which were not considered to be clinically significant by the sponsor. The complement decreases were not associated with study drug-related AEs during the corresponding infusions for either subject, and no clinical signs of complement consumption were observed. The

antibody levels over 72 week of treatment for each subject are represented graphically in the following figure (electronically copied and reproduced from the sponsor's submission).

**Figure 18. Anti-galsulfase antibodies in subjects treated with galsulfase in Study 01-04**




Interruptions in lines are due to a missing data point (specimen not collected).
Reference: Data from Listing 16.2.10 were graphed using SigmaPlot

Subject 304 did not have detectable anti-galsulfase antibody levels through the 72 weeks of the study. Because this is the only subject with adequate follow up post-galsulfase exposure that did not raise anti-galsulfase antibodies, further analysis was conducted to investigate potential causes. No obvious reasons for the lack of antibody formation were identified: the subject had received Prednisone eye drops to the left eye for the initial phase of the study (from baseline and up to week 40), but this would likely be insufficient to blunt an immune response to galsulfase. The subjects endogenous sulfatase enzyme activity was 0.12 pmol/min/mg in leukocytes and 0.17 pmol/min/mg in cultured skin fibroblasts, levels that are consistent with other patients with MPS VI, and in whom anti-galsulfase antibodies were detected.

### 10.1.3.4.1.2.4 Clinical Laboratory Findings and Vital Signs

The most commonly observed abnormal laboratory results were elevations above the upper limit of normal (ULN) in lactic dehydrogenase (LDH), alkaline phosphatase (alk phos) and aspartate aminotransferase (AST). The majority of subjects had elevations in these enzymes at baseline, and there was little change over the 72 weeks of the study. Only one subject (Subject 300) developed any elevation in these enzymes >2 X ULN, which was in LDH on 4 occasions. The subject's baseline LDH levels were also elevated, but not to this magnitude. There were no other notable laboratory abnormalities during the study.

There were no notable changes in vital signs during the course of the study, other than the 2 reports of hypotension during study drug infusion as noted above.

10.1.3.5 Conclusions

MPS VI is a rare disease with a wide range of disease severity and disease progression, and interpretation of this study is limited by the small size of the study, the lack of a control group, and a lack of established measures of clinical efficacy. Thus, these results should only be considered as supportive of the larger study submitted to this BLA. The study did show some encouraging results, however, especially a consistent pharmacodynamic effect of the enzyme and increases in endurance in all subjects. There was also a lack of evidence for significant deterioration in most subjects during the 72 weeks of the study; however, it is noted that for the most debilitating aspects of the disease, such as respiratory abnormalities and joint restriction, no clinical benefit of galsulfase treatment could be demonstrated. Treatment was also shown to be generally well-tolerated by the subjects, with all 10 subjects completing the study and receiving all but 3 weekly infusions (in 2 subjects) of study medication over the 72 week duration of the study. All subjects experienced at least 1 AE during the study, but most AEs were likely to have been secondary to the underlying disease.

10.1.3.6 Summary

The efficacy and safety results for Study ASB-01-04 are summarized as follows:

The efficacy results showed that:

- Urinary GAGs levels decreased in all subjects by Week 6 and remained decreased throughout the 72-week treatment period, a result consistent with a pharmacodynamic effect of the enzyme. Further supporting this pharmacodynamics effect, all subjects but 1 had decreases in liver volume, and all subjects except 2 had decreases in spleen volume at Week 48.
- For the 12MWT and the Stair Climb test, the 2 primary endpoints that were measures of endurance, the results showed that all subjects had improvement from baseline at Week 48 in both tests. However, in the 12MWT, a training effect was demonstrated, and the magnitude of improvement was related to the distance walked at baseline (subjects with the lowest scores at baseline showed the highest percent increases in distance walked and subjects with the highest scores showed the lowest percent increases in distance walked). For the Stair Climb test, there was no association with increases in stairs climbed at Week 48 and baseline score, but a training effect could not be ruled out. Nonetheless, as MPS VI is a progressive disease that would be expected to show deterioration rather than improvement over time, the results are at least suggestive of an improvement in endurance with study drug treatment.
- The results for many of the other efficacy measures were harder to interpret. The ETGG test showed a decrease in time for 9 of 10 subjects, but the clinical relevance of these test results to MPS VI is unknown. Active and passive shoulder ROM, grip strength and pinch strength test results showed no consistent change from baseline. For the MPS QoL Profile, only 1 of the 4 tests in the profile was able to be performed consistently, the clinical relevance of which is unknown. The Childhood and Adult

Pain and Joint Stiffness Questionnaires are highly subjective tests, results of which should be interpreted with caution as this was an open-label uncontrolled study.

- The secondary endpoints were notable for no consistent changes in PFTs from baseline at Week 72, ECGs, echocardiograms or bone mineral density from baseline at Week 48, and no notable changes in visual exams or oxygenation during sleep. Linear growth was demonstrated in 8 of 8 subjects with results at baseline and at Week 72 (Week 72 measurement not performed in 2 subjects), and pre-pubertal subjects had the largest increases in height; however, growth velocity prior to study drug administration is unknown making it difficult to discern an effect of study medication.

The safety results showed that:

- Overall, treatment was generally well tolerated and all subjects were able to receive all but 3 of their weekly study drug infusions (in 2 subjects) over the 72 weeks of the study. There were no deaths or discontinuations of study drug due to AEs (or any other reason) during the study.
- All subjects experienced at least 1 AE during the study, the majority of which were likely due to underlying disease; however, as this was an open-label, uncontrolled study, no assessment of study drug's effect on the incidence of AEs can be performed. The most commonly reported AE terms were infection (10 subjects), URI/rhinitis (9), arthralgia (8), and headache (6). Serious AEs occurred in 4 subjects, and only the terms pneumonia (2) and sleep apnea (2) occurred in more than 1 subject, both of which were likely secondary to underlying disease.
- Anaphylactoid reactions occurred in 2 subjects, and included the AEs of chills, fever, urticaria, prostration, hypotension, vomiting and rash. Despite these AEs, both of these subjects were able to receive all of their study drug infusions with slowing or interrupting the infusions, and with treatment with antihistamines or other medications.
- Anti-galsulfase antibodies were measurable in 9 of 10 subjects. The 3 subjects with the highest antibody levels were noted to have the highest urinary GAGs levels throughout most of the study, implying some neutralization of study drug effect. These 3 subjects were not noted to have any anaphylactoid reactions, or other clinically noteworthy effects attributed to the antibody formation.
- There were no notable clinical laboratory findings.

## 10.2 Line-by-Line Labeling Review

### 10.2.1 Issues

The labeling issues and the editing of the package insert are currently under review and internal discussion among the different Divisions involved in the review of this application.

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