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

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: 125117 / 0 4/26/05

Drug Name: Galsulfase, solution for intravenous infusion, 1.0 mg/kg administered once weekly as an intravenous infusion over a 4-hour period.

Indication(s): /

Applicant: BioMarin Pharmaceutical Inc.

Date(s): Receipt date: November 29, 2004. Filing due date: January 28, 2005. First Action Due Date: May 31, 2005.

Review Priority: Priority

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Keywords:

baseline imbalance, clinical studies, double-blind, longitudinal data analysis, multi-center, randomization, sensitivity analysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Efficacy Conclusions:

Based on an evaluation of the applicant's analysis and an additional sensitivity analysis of the Phase 3 study ASB-03-05, this reviewer concludes that the results for the primary efficacy endpoint were reasonably robust to different approaches to the statistical analysis. The results from the statistical analysis support the applicant's conclusion that Galsulfase is superior to the placebo with respect to the average improvement in 12 minute walk distance between week 24 and baseline (Table 5). Results from the statistical analysis of secondary and tertiary efficacy endpoints were also supportive of the overall conclusion that Galsulfase was superior to the placebo in improving the level of physical endurance in patients with MPS VI. Results from the open label extension of study ASB-03-05 were consistent with the interpretation that the placebo patients were able to improve their 12 minute walk distance after they were switched to Galsulfase.

Safety Conclusions:

The applicant has included a warning about infusion reactions in the draft labeling text, and a description of adverse reactions. These appear to be appropriate from a statistical perspective, given the findings on adverse events and infusion-associated reactions.

Recommendations:

This reviewer provided recommendations for revising the draft labeling text and tables concerning the results of the 12 minute walk test and the 3 minute stair climb. These recommendations are provided for additional clarity, and are summarized in Tables 8, 10 and 12 of this review.

1.2 Brief Overview of Clinical Studies

Galsulfase (rhASB) is proposed to be indicated in the treatment of patients with MPS VI disease. The evaluation of the effectiveness and safety of Galsulfase is based on one Phase 3 double-blind study, one Phase 1/2 double-blind, controlled, dose-comparison study, and one Phase 2 open label study. A total of 56 patients with MPS VI were enrolled in these three studies; 36 received Galsulfase and 20 received placebo. Baseline demographic and disease characteristics for the three study populations were comparable. The Phase 1/2 dose comparison in 7 patients evaluated 0.2 vs. 1.0 mg/kg for 24 weeks. Subsequent open label treatment at 1.0 mg/kg continued for 144 weeks. A Phase 2 open label study in 10 patients assessed treatment with 1.0 mg/kg over an initial 24 weeks. Subsequent treatment at 1.0 mg/kg continued for 72 weeks.

The pivotal Phase 3 clinical study was a randomized, placebo-controlled clinical trial of 39 MPS VI patients. The study involved six centers, located in the U.S., Germany, England, Brazil, France and Portugal. Nineteen patients were randomized to receive Galsulfase and 20 patients were randomized to receive placebo. Patients received weekly, double-blind, intravenous infusions of either Galsulfase at 1.0 mg/kg or placebo solution for 24 consecutive weeks. The primary efficacy outcome assessment was the distance walked in 12 minutes. The statistical conclusions are primarily based on the analysis of the pre-specified primary efficacy variable, with supportive information from secondary and tertiary efficacy variables. The sponsor also included data on the 12 minute walk and 3 minute stair climb from weeks 24 to 48 of the open label extension of the Phase 3 study.

1.3 Statistical Issues and Findings

This reviewer explored, examined, and analyzed the applicant's data from the Phase 3 study and its open label extension. This reviewer verified the applicant's findings for the primary efficacy variable and conclusions. In addition to assessing the sensitivity analysis conducted by the applicant, this reviewer confirmed the robustness of the statistical results by using additional statistical approaches to the analysis of the primary efficacy variable.

Because of a concern about an imbalance in the Phase 3 study in the baseline 12 minute walk distance, this reviewer assessed the allocation process as reported in the application. This reviewer concludes that the process was adequate, provided that the BioMarin personnel who assigned the ID codes to eligible patients were not aware of the list that linked the ID code to the treatment assignment.

The Phase 3 study was small (39 MPS VI patients total, with 19 allocated to Galsulfase) because MPS VI is a relatively rare disorder. The small study may limit the extent to which the results can be generalized to the target population. However, this reviewer notes the consistency of

supportive findings in the secondary and tertiary efficacy variables and from the open-label extension of the study.

2. INTRODUCTION

2.1 Overview

Mucopolysacharidosis

Mucopolysaccharidosis (MPS) is a particularly well-defined subgroup of lysosomal storage disorders in which each type of MPS is caused by the deficiency of a special lysosomal enzyme required for the catabolism of glycosaminoglycans (GAGs). MPS VI, or Maroteaux Lamy Syndrome, is a serious, debilitating, life-threatening disease that is caused by the deficiency of the lysosomal enzyme, *N*-acetylgalactosamine 4-sulfatase (Arylsulfatase B; ASB). 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. Infants with the disease appear normal at birth but come to clinical attention at 6-24 months of age due to progressive deceleration of growth, skeletal deformities, coarse facial features, upper airway obstruction and joint deformities. Progressive clouding of the cornea, communicating hydrocephalus and heart disease can also develop in MPS VI children. Death usually results from respiratory infection or cardiac disease. Although MPS VI is usually fatal by the teenage years in subjects with the most rapidly advancing disease, those with more slowly advancing disease may survive into their 4th decade. This variation in the development of clinical symptoms provides the basis for the large phenotypic heterogeneity characteristic of the disease.

Approximately 1100 individuals worldwide have MPS VI, with an estimated number of patients in the U.S. between 50 and 300. The applicant claims that there is no satisfactory treatment for MPS VI. A few patients have benefited from bone marrow transplantation (BMT). Other than BMT, most patients receive symptomatic care for specific progressive symptomatic problems as their only form of care.

Class and Indication

The investigational product is Galsulfase, or recombinant human *N*-acetylgalactosamine 4-sulfase (rhASB). The proposed indication is for treatment of MPS VI. Galsulfase is an enzyme produced by recombinant DNA technology that is analogous to the normal human enzyme. The rationale for Galsulfase therapy is to provide exogenous enzyme that will be taken up into lysosomes and increase the catabolism of GAGs. The applicant notes that treatment with Galsulfase offers the potential for improvements in disease-associated pathophysiologies such as cardiopulmonary function, joint range of motion, and pain. Improvement in endurance is also expected, where "endurance" is viewed as a composite measure of the effect of Galsulfase on

multiple organ systems and disease-associated pathophysiologies. The applicant predicts that the clinical improvement with Galsulfase treatment would decrease the overall need for symptomatic treatment. These specific clinical benefits of Galsulfase may result in improved endurance, quality of life and increased lifespan.

History of Drug Development

The Galsulfase dose and regimen, as well as key clinical endpoints were established in Phase 1 and 2 studies. The dosage regimen of 1.0 mg/kg for weekly intravenous infusions was supported by the results of a Phase 1/2 study in 7 MPS VI patients. This study also supported the use of the 6-minute walk test as a measure of endurance, encompassing musculoskeletal, cardiovascular and pulmonary components. In addition, this study supported the use of Urinary GAG levels to indicate the improvement in the biochemical manifestation of MPS VI.

Results from a one-time assessment of 121 MPS VI patients in a survey study suggested that impaired endurance affected the entire spectrum of slowly to rapidly advancing disease, and also documented that urinary GAG levels are an important indicator of morbidity.

The Phase 3 study reported in this application (ASB-03-05) is a 24 week, double-blind, placebo-controlled study with 19 patients randomized to Galsulfase and 20 patients randomized to placebo, with efficacy and safety data up to week 24. The open label extension of this Phase 3 study, ASB-03-06, continues with open label treatment of 38 patients with Galsulfase. Preliminary analysis of endurance and respiratory function data from 24 weeks of the study is included in this application.

Specific Studies Reviewed

The Phase 3 study ASB-03-05 was selected for a full statistical review and evaluation because it is the only Phase 3 controlled, randomized study in this application. Data from this study may provide most of the substantial evidence for efficacy and safety of Galsulfase for this proposed indication. In addition, FDA requested that BioMarin provide data from the 12 minute walk and the stair climb from the first 24 weeks of the open label extension of study ASB-03-05 (study ASB-03-06). The reason for this request was to help interpret the results from the primary efficacy variable (the 12 minute walk) in study ASB-03-05. This study had an imbalance at baseline between the two randomized groups in the performance of the 12 minute walk test. The medical reviewers believed that an assessment of patients' response after being switched from placebo to Galsulfase in the open label extension may assist in interpreting the results from the randomized, controlled part of the study. For this reason, the full statistical review will include the data on 12 minute walk and stair climb from the first 24 weeks of the open label extension of study ASB-03-05.

Below are descriptions of all studies described in this application.

Study ASB-00-01: "A Phase 1/2 randomized, double-blind, two dose group study of rhASB enzyme replacement therapy in patients with MPS VI." Seven patients were enrolled in the study, which was conducted at seven centers in the U.S. Patients were randomized to one of two dose levels, 0.2 mg/kg (4 patients) and 1.0 mg/kg (3 patients), for weekly intravenous infusions. An interim analysis of unblinded safety and efficacy data of treatment for each patient was performed after the sixth patient enrolled completed 24 weeks of treatment. Following this interim analysis, all patients that had been randomized to the lower dosage were transitioned to the higher dosage for the rest of the study. Six of the seven enrolled patients successfully completed the first 24 weeks of the study, and five patients were on study at week 144.

The efficacy of 2 dosage levels of Galsulfase was assessed by periodic assessments of the 6-minute walk test, pulmonary function, urinary GAG, standing height, weight, grip strength, pinch strength, cardiac function, hepatomegaly, bone mineral density, along with clinical assessments from chest and cervical spine X-rays, sleep studies, visual exams, and health assessment questionnaires.

Safety was assessed by documenting all adverse events that occurred during the study. Safety was also assessed by the measurement of vital signs, pulse oximetry and cardiorespiratory monitoring at every study visit. The study schedule also included physical examinations, fasting serum chemistry and hematology laboratory studies, anti-rhASB antibody studies and measurement of complement activation.

Study ASB-00-02: "A survey study of subjects with MPS VI." The objective of the study was to establish the range and diversity of clinical symptomatology in selected subjects diagnosed with MPS VI. The survey study was conducted in 7 countries at centers with expertise in evaluating and treating individuals with MPS VI. Clinical and biochemical parameters known to affect MPS VI individuals were evaluated at a single time point in 123 subjects (2 of these were later determined not to have MPS VI). These parameters include endurance (6-minute walk test), respiratory function, urinary GAGs and dermatan sulfate, active joint range of motion, grip and pinch strength, physical exam, health assessment questionnaire, and past medical history. Sleep studies and echocardiograms were performed at certain sites.

Study ASB-01-04: "A Phase 2 open label clinical study of the efficacy and safety of recombinant human rhASB enzyme replacement therapy in patients with MPS VI." The ten patients were enrolled in this study were treated at one of two primary centers, one center in the U.S. (five patients) and one center in Australia (five patients). To be eligible, patients had to be 5 years of age or older, with documented diagnosis of MPS VI, and able to walk at least 1 meter but no more than 250 meters in the first six minutes of the 12 minute walk test at baseline. Patients were treated at a primary center for at least the first 6 weeks; thereafter, patients could be treated at a center close to their home. Patients returned to their primary center at weeks 12, 24, 48 and every 24 weeks thereafter, and at early termination, for specified efficacy and safety measurements. Interim analyses of efficacy and safety data were conducted after the 10^{th} patient

completed 12 and 24 weeks of study therapy. Patients who completed the first 24 weeks of treatment were offered a continuation of the therapy until a regulatory decision was made concerning the status of the drug, or until the applicant terminated the study.

Efficacy variables included measurements of endurance and mobility: Expanded timed get-up and go test, shoulder range of motion, stair climb test, 12 minute walk test, grip and pinch strength, childhood and adult pain and joint stiffness questionnaires, and MPS VI quality of life profile. These variables were assessed at weeks 6, 12, 24 and 48. Urinary GAG levels were measured at weeks 1, 4, 6, 8, 12 and every 6 weeks thereafter through week 72. The study is ongoing at the time of this application. Other efficacy variables were also measured. The clinical safety was assessed using serial physical examinations, vital signs, anti-rhASB antibodies, measurement of complement activation, clinical laboratory parameters, ECGs, and the incidence and severity of adverse events.

Study ASB-03-05: "A Phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational clinical study of rhASB in patients with MPS VI." The primary objective of the study was the 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 minute walk test at week 24 compared with baseline. This study involved six centers, of which 1 was in the U.S. A list of centers and number of patients in each group is as follows:

Study Center	Number of patients	
	Galsulfase	Placebo
Children's Hospital & Research Center, Oakland, CA, USA [1]	2	4
Kinderklinik und Kinderpoliklinik der Johannes-Guttenberg-Universitaet, University of Mainz, Mainz, Germany	4	4
Royal Manchester Children's Hospital, Pendlebury, Manchester, England	3	3
	4	4
	2	3
	4	2
Totals	19	20
[1] 16.7% (6 out of 39) of patients in the study were at the U.S. site. 10.5% (2 out of 19) of patients treated with Galsulfase were at the U.S. site.		

To be eligible, a patient had to be at least 7 years of age with a diagnosis of MPH VI. The patient had to be able to walk independently, at least 5 meters and no more than 270 meters in the first 6 minutes, or no more than 400 meters total in 12 minutes, in the screening 12 minute walk test. Other inclusion / exclusion criteria are described in more detail in the application. Patients underwent eligibility assessments during a 1- to 2-week screening period at 1 of 6 primary sites. Following the determination of eligibility, patients underwent baseline assessments during a 2 week baseline period. Eligible patients were then randomized (in a 1:1 ratio) to either the Galsulfase treatment group or a placebo control group.

Patients received weekly, double-blind IV (intravenous) infusions of either Galsulfase 1.0 mg/kg or placebo solution for 24 consecutive weeks. Patients remained in close proximity to the primary site for the 24-week study period. All assessments were conducted at the primary site. After 24 weeks, all patients were eligible to receive Galsulfase in a separate open label extension study (Study ASB-03-06).

The primary efficacy endpoint was the 12 minute walk test, which was performed as a measure of endurance. The test was performed once to screen for eligibility prior to enrollment and randomization, and twice (i.e., on 2 separate days), at each of the following timepoints: baseline and weeks 6, 12, 18 and 24. Patients were instructed to walk as far as possible in 12 minutes. The distance walked in meters was recorded at 6 and 12 minutes.

Secondary efficacy endpoints were the 3 minute stair climb and urinary GAG levels. Tertiary efficacy endpoints included assessment of joint pain, joint stiffness and physical energy level, shoulder range of motion, coin pick-up test and visual acuity. These were all measured on a similar schedule as the 12 minute walk test. In addition, several clinical parameters were evaluated at baseline to provide additional evidence for the severity of disease prior to treatment and to allow for long-term evaluation of Galsulfase treatment. These parameters include cardiac function, respiratory function, the status of the cornea, optic nerve and retina, and the utilization of health resources.

Safety was assessed by medical history, physical examinations, measurement of vital signs, serial assessments of MPS VI signs and symptoms, recording of adverse events, serial assessment of immunologic parameters (antibody and complement levels), and monitoring of changes in laboratory parameters (chemistry, hematology and urinalysis). Electrocardiography and thyroid function tests were also conducted. An independent Allergic Reaction Review Board reviewed severe or serious infusion-associated reactiosn (IARs) during the study.

Study ASB-03-06: "A multicenter, multinational, open label extension study of rhASB in patients with MPS VI." This study is the open label extension of the Phase 3 study ASB-03-05. Patients from ASB-03-05 began treatment in the extension study during the 25th week but no later than the 26th week following initiation of their treatment in the Phase 3 study ASB-03-05. All patients received infusions of Galsulfase 1.0 mg/kg administered intravenously over approximately a 4-hour period once a week. Patients and physicians entered this study blinded to their treatment assignments in study ASB-03-05. Patients returned to the primary site for assessments in the 12 minute walk test and the 3 minute stair climb at weeks 36 and 48.

Major Statistical Issues

The average 12 minute walk was greater in the placebo group than the Galsulfase group at baseline (see Figures 1 and 2 in this review). The difference at baseline between the groups was

nearly twice as great as the estimated effect of galfulase on the 12 minute walk distance. This imbalance led to a concern from the medical perspective that the placebo group may have been at a plateau of performance with respect to the 12 minute walk, and the Galsulfase group may have shown improvement in part because of regression to the mean. Because of this concern, it became important to review the results from the open label extension portion of study ASB-03-05. These results supported the medical interpretation that the improvement in 12 minute walk at week 24 in the Galsulfase group, relative to the placebo group, could reasonably be attributed to the effect of Galsulfase. This issue is discussed in more detail in section 3.1.

From a statistical perspective, the imbalance at baseline does not influence the validity of the analysis model used in estimating the effect of Galsulfase, as long as the patients were indeed assigned at random (see Chapter 7 in Senn, 2000[1] for a discussion of this issue). For this reason, the process used in assigning patients to treatment was evaluated carefully. This issue is discussed in more detail in section 3.1. The credibility of the comparison between groups at 24 weeks would also be improved if there was considerable overlap between the two groups in the distribution of 12 minute walk distances at baseline. The extent of this overlap was evaluated, and these results are presented in section 3.1.

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CBER Electronic Document Room (EDR). The submission is recorded in the EDR as indicated in Table 1. All the data submitted are in SAS v.5 transport format. The number of data files for the pivotal studies and the number of data files used in the statistical review are shown in Table 1.

Table 1. Data sources

Document: STN 125117/0	
CBER EDR link: \\CBS5042329\M\EDR Submissions\2004BLA\DCC60000290\roadmap.pdf	
Letter Date: 11/23/2004	Stamp Date: 11/24/2004
Company: BioMarin	
Drug: Galsulfase, recombinant human N-acetylgalactosamine 4-sulfatase (rhASB)	
Path \crt\datasets\asb-03-05\ \crt\datasets\asb-03-06\	

[1] Senn, S. 2000. *Statistical Issues in Drug Development.* Chapter 7: Baselines and Covariate Information. NY: Wiley.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The focus of the efficacy evaluation is on the Phase 3 study ASB-03-05 with additional information from the open label extension, study ASB-03-06.

The process of allocating patients to treatment groups

The allocation process was the focus of review because the study results showed a large imbalance in average 12 minute walk distance at baseline (Figures 1 and 2). This reviewer wanted to make sure that the allocation process would provide a reasonable basis for the statistical comparison between Galsulfase and placebo. BioMarin also summarized their evaluation of this process in their application materials.

The randomization process is summarized as follows: Personnel at BioMarin assigned an ID code to a patient on request from a study investigator, after eligibility was confirmed. The study investigator then obtained a treatment assignment from a list that matched the ID code to a treatment group. This list was provided by → , and accessed through an Interactive Voice Response (IVR) system. For each site, treatment group assignment was randomized in a sequence of two blocks of two followed by blocks of four. After reviewing the information in the application, this reviewer concluded that the blocked randomization and the separation of function would provide a reasonable basis for a random allocation, as long as the BioMarin staff were not aware of the treatment assignments linked to the ID code.

This reviewer concludes that the process that BioMarin used to allocate patients to groups was adequate, provided that the BioMarin personnel who assigned the ID codes to eligible patients were not aware of the list that linked the ID code to the treatment assignment.

However, BioMarin reviewed the implementation of randomization procedures at each site and concluded that the non-parametric randomization test of the 12-minute walk distance would not have a valid p-value. This test was described in the Statistical Analysis Plan as a comparative exploration to the longitudinal analysis. BioMarin implemented this distribution-free test by randomly selecting the entry order of patients 100,000 times and allocating them according to the pre-specified randomized block scheme. However, the sites entered patients into the study in an order that was determined by a combination of their screening walk distances, their overall physical status, and the convenience of scheduling, rather than the order given in the sequence of randomized blocks assigned to each site. Because of these circumstances, BioMarin determined that it was not possible to enumerate the actual sample space for the test, and therefore the p-value from the randomization test was not valid.

Baseline 12 minute walk

There was a considerable overlap in the distribution of 12 minute walk distances at baseline between the placebo group (mean 364.5, minimum 45.5, maximum 685.0) and the Galfulase group (mean 226.7, minimum 9.2, maximum 623.3); Figure 1. This overlap provides assurance that the statistical comparison between the two groups at 24 weeks is credible in spite of the difference in average 12 minute walk distance at baseline.

Disposition of patients

All 39 patients randomized received some study drug, either Galsulfase or placebo. All but one patient stayed in the study through the full 24 weeks. Patient 020-006 dropped out of the study after the week 5 infusion. This patient withdrew his informed consent and did not provide a reason.

Selected patient demographic and baseline characteristics

The study patients ranged in age from 5 to 29 years; two-thirds of the patients were female. The racial/ethnic composition (62% white, non-Hispanic; 10% Hispanic; 28% other) was consistent with the demographic distribution of the particular sites enrolling patients. The racial composition of the 2 groups differed somewhat, with 15 of the 19 Galsulfase patients (79%) defined as white and 9 of the 20 placebo patients (45%) so defined (refer to Table 2).

Table 2. **Distribution of sex and race** (Obtained from Table 11-3 of the application.) For a definition of the walk-eligible subset and the ≤ 400 m subset, see text, under "The analysis datasets."

	rhASB	Placebo
	n (%)	n (%)
All Patients	**N=19**	**N=20**
Sex (proportion male)	7 (37)	6 (30)
Race (proportion white)	15 (79)	9 (45)
Walk-Eligible Subset	**n=17**	**n=15**
Sex (proportion male)	7 (41)	5 (33)
Race (proportion white)	13 (76)	8 (53)
≤400 m Subset	**n=16**	**n=12**
Sex (proportion male)	6 (38)	4 (33)
Race (proportion white)	13 (81)	6 (50)

While most characteristics were well balanced at baseline, the placebo patients were, on average, younger (mean age placebo: 10.7 yrs; Galsulfase: 13.7 yrs) and lighter than the Galsulfase patients (mean weight placebo: 20.8 kg; Galsulfase 24.6 kg) (refer to Table 3).

Table 3. **Selected baseline characteristics** (Obtained from Table 11-4 in the application). For a definition of the walk-eligible subset and the ≤ 400 m subset, see text, under "The analysis datasets."

Group/ Baseline Characteristic	rhASB			Placebo		
	n	Mean	SD	n	Mean	SD
All Patients						
Age (years)	19	13.7	6.47	20	10.7	4.35
Standing height (cm)	19	104.4	12.87	20	100.3	13.54
Sitting height (cm)	19	57.0	14.07	19	55.8	11.22
Weight (kg)	19	24.6	9.14	19	20.8	7.85
Walk-Eligible Subset						
Age (years)	17	14.4	6.53	15	10.5	4.29
Standing height (cm)	17	105.6	13.08	15	96.2	10.12
Sitting height (cm)	17	58.8	13.26	14	55.7	12.17
Weight (kg)	17	25.7	9.13	14	19.4	5.20
≤400 m Subset						
Age (years)	16	14.4	6.73	12	10.6	3.94
Standing height (cm)	16	104.3	13.37	12	97.1	12.05
Sitting height (cm)	16	56.9	15.25	11	53.8	12.27
Weight (kg)	16	25.3	9.42	12	20.1	5.31

The analysis datasets:

There was very little missing data in study ASB-03-05. The ITT data set included all randomized patients. Because all but one patient stayed in the study through the full 24 weeks, this reviewer did not expect that alternative methods of imputation would have a substantial impact on the statistical results.

The applicant made the following decisions about the ITT database concerning situations that arose during the study:

(1) Patient 020-006 dropped out of the study after the week 5 infusion. All of the longitudinal analyses of the ITT population include this patient. The post-treatment values for this patient were imputed from the solution coefficients of the primary analysis model for the placebo group, adjusted for Patient 020-006's baseline value. The applicant describes this approach as imputation "along the trajectory of the other placebo patients."

(2) Patient 021-006 was sick on the day of the second assessment at week 24. For this reason only the first assessment day was used in calculating the 12 minute walk distance at week 24 for this patient.

(3) The data analysis plan included a rule for a 2-week window on both sites of a scheduled visit was allowed for patients to complete protocol-defined assessments. However, the applicant allowed an additional 3 days beyond this window if one of the visits fell within the window.

Because of the concern with the baseline imbalance in 12 minute walk distance between the two groups, the applicant constructed two subsets of the ITT database. The "Walk-Eligible Subset" included the 32 patients who satisfied the eligibility requirements with respect to their screening walk test results (not more than 270 m in 6 minutes or not more than 400 m in 12 minutes). This subset excluded 7 patients who walked somewhat further than 400 m in the screening 12 minute walk but who were still included in the study. Five of the 7 excluded patients had been allocated to the placebo group. The "$\leq$ 400 m Subset" included only the 28 patients who walked $\leq$ 400 m in 12 minutes at baseline. The applicant analyzed the primary and secondary efficacy variables in these two subsets.

This reviewer concludes that the applicant made reasonable decisions concerning the Intention-To-Treat (ITT) data set, the methods used to impute or otherwise allow for missing data or mis-timed data, and the selection of subsets of the data for additional analysis.

Primary efficacy endpoint: 12 minute walk

The applicant's primary statistical analysis model (Model 1) was selected in concurrence with the Agency, prior to unmasking the data. This was a repeated measures linear model with baseline 12 minute walk distance as a covariate. The dependent variable was the average distance from the 12 minute walk test on the two testing days. The equation for Model 1 is given below, with additional description provided by the applicant:

Model 1. Primary efficacy analysis model used by BioMarin

$$E(Y) = \beta_0 + \beta_1 BL + \beta_2 Trt + \sum_{i=1}^{5} \beta_{3i} Site_i + \beta_4 W_6 + \beta_5 W_{12} + \beta_6 W_{18} + \beta_7 W_6 \times Trt + \beta_8 W_{12} \times Trt + \beta_9 W_{18} \times Trt$$

where Y is the distance walked in the 12 minute walk; β_0, β_1, β_2, and β_{3i} are coefficients for the intercept, baseline 12 minute walk measurement (BL), treatment (Trt) and sites (Site *i*),

respectively, where Site 6 is the reference site; β_4, β_5, and β_6 are coefficients for the times of measurement at Weeks 6, 12, and 18 with Week 24 as the reference; and β_7, β_8, and β_9 are coefficients for the week by treatment interaction terms. Restricted maximum likelihood (REML) will be used to estimate the parameters. With this parameterization, β_2 is the treatment effect comparing the difference between treated and placebo groups at Week 24, adjusted for baseline. A test of the null hypothesis (H0: $\beta_2 = 0$) tests the difference between treated and placebo groups at Week 24 versus the difference between treated and placebo groups at baseline.

In order to develop an understanding of Model 1 and to illustrate the use of additional models in a sensitivity analysis, this reviewer re-expressed Model 1 in more general terms as an analysis of variance model. The re-expression uses an over-parameterized version of Model 1 in order to express each factor and interaction separately with the full set of factor levels. This re-expression is shown as Model 2 below:

Model 2. A re-expression of Model 1 developed by this reviewer

$$Y_{ijkt} = \mu + \beta X_{i0} + \gamma_j + \alpha_k + \tau_t + \alpha\tau_{kt} + \varepsilon_{i(jk)} + \varepsilon_{it(jk)}$$

where Y_{ijkt} is the 12 minute walk distance for subject i at site j, treatment group k and week t. The terms μ, β, γ, α, τ, and $\alpha\tau$ represent the overall mean, the covariate effect of the pre-treatment baseline 12 minute walk, the fixed effect of site (j = 1 to 6), the fixed effect of treatment group (k = 0 for placebo, 1 for rhASB), the fixed effect of post-treatment weeks (t = 6, 12, 18, 24), and the interaction of treatment group and weeks, respectively. The terms $\varepsilon_{i(jk)}$ and $\varepsilon_{it(jk)}$ represent among-subject and repeated measures (within-subject) error, respectively. A compound symmetry structure for the covariance matrix was specified.

Model 1 was fit using SAS® PROC MIXED, and the results are summarized in Table 4. Figure 2 shows the observed and the adjusted treatment means by week.

This reviewer confirmed the statistically significant difference between the Galsulfase group and the placebo group (p=0.025) for the 12 minute walk distance at week 24, based on the adjustment for a common baseline, obtained from Model 1 and the ITT data. The results from Model 2, used by this reviewer, were the same as the results reported from Model 1 by the applicant. The patients in the Galsulfase group showed an improvement in walk distance at week 24 that was 92 meters greater than the improvement showed in the placebo group (Tables 4 and 5). The common baseline 12 minute walk was 306 m (Figure 2).

The applicant conducted an extensive sensitivity analysis, using the ITT as well as the "Walk-Eligible" and "≤ 400 m" subsets of the data, and different versions of Model 1. In general, the

variations of Model 1 excluded and/or added different terms and used different specifications for the covariance matrix. The model variations and results from the sensitivity analysis are summarized in Table 6. On the basis of the primary analysis and the sensitivity analysis, the applicant concluded that "The primary efficacy endpoint, a statistically significant difference in mean distance walked in 12 minutes between the Galsulfase and placebo group, was met. The Galsulfase group walked a mean ± SE of 92 ± 40 m further than the placebo group at Week 24 (p-value = 0.025). This clinically significant difference in means confirms the ability of Galsulfase to improve endurance in MPS VI patients. The p-values for the Walk-Eligible and ≤ 400 m subsets were 0.016 and 0.024, respectively. Additional sensitivity analyses confirmed the robustness of the results of the primary analysis."

This reviewer conducted an additional sensitivity analysis, using two analysis models, in order to evaluate the robustness of the study conclusions further. Model 3 is an analysis of covariance model that uses a subset of the ITT data, consisting of data from week 24 and week 0 (baseline) only. The dependent variable is the difference between week 24 and baseline 12 minute walk distance, and the model includes the baseline walk distance as a covariate:

Model 3. **An analysis of covariance model used by this reviewer in a sensitivity analysis.**

$$Y_{ijk24} - Y_{ijk0} = \delta + \beta X_{i0} + \gamma_j + \alpha_k + \varepsilon_{i(jk)}$$

where $Y_{ijk24} - Y_{ijk0}$ is the difference between the 12 minute walk distance at week 24 and at baseline (week 0) for subject i at site j and treatment group k, δ represents the overall difference, and the remaining terms are as described for Model 2. Model 3 is an analysis of covariance and does not have a repeated measures structure.

Model 4 evaluates the slope formed by the regression of 12 minute walk distance on week for each subject separately. Model 4 is fit in two steps. In step one, a separate slope for each subject is estimated from the linear regression of 12 minute walk distance on week (weeks 0 to 24). In step two, the slopes from all subjects are combined in an analysis of variance model with slope as the dependent variable:

Model 4. **An analysis of slopes model used by this reviewer in a sensitivity analysis.**

$$b_{ijk0to24} = \lambda + \gamma_j + \alpha_k + \varepsilon_{i(jk)}$$

where $b_{ijk\,0to24}$ is the slope estimated for subject i at site j and treatment group k, obtained from the linear regression of 12 minute walk distance on weeks 0 to 24, λ represents the overall slope, and the other terms are as described for Models 2 and 3.

The results from the additional sensitivity analysis that this reviewer conducted support the applicant's conclusion that the Galsulfase group had a greater increase in 12 minute walk distance than the placebo group (Table 5). The results from Model 3, using only weeks 24 and baseline, were similar to those from Models 1 and 2. The results from Model 4 showed a positive average slope for the Galsulfase group, consistent with an increase in 12 minute walk distance over time, and a relatively horizontal average slope for the placebo group. While the p-value for the comparison between groups was not significant at p=0.054, the findings support the applicant's conclusions.

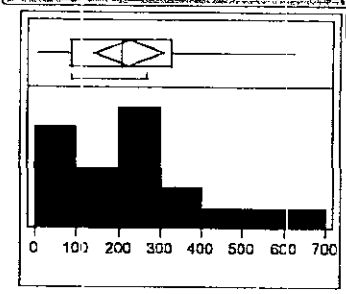
Based on an evaluation of the applicant's analysis and an additional sensitivity analysis, this reviewer concludes that the results for the primary efficacy endpoint were reasonably robust to different approaches to the statistical analysis. The results from the statistical analysis support the conclusion that Galsulfase is superior to the placebo with respect to the average improvement in 12 minute walk distance between week 12 and baseline.

Figure 1. Summary of baseline 12 minute walk distances for Galsulfase and placebo groups. Treatment arm "A" is Galsulfase and treatment arm "P" is placebo.

Randomization Treatment Arm=A

Distributions

Total distance walked in 12 minutes (meters)



Quantiles

100.0%	maximum	623.25
99.5%		623.25
97.5%		623.25
90.0%		508.00
75.0%	quartile	330.00
50.0%	median	210.25
25.0%	quartile	90.00
10.0%		22.50
2.5%		9.20
0.5%		9.20
0.0%	minimum	9.20

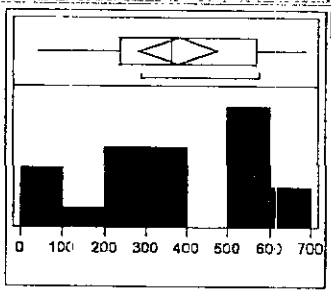
Moments

Mean	226.69211
Std Dev	170.42268
Std Err Mean	39.097645
upper 95% Mean	308.83321
lower 95% Mean	144.551
N	19

Randomization Treatment Arm=P

Distributions

Total distance walked in 12 minutes (meters)



Quantiles

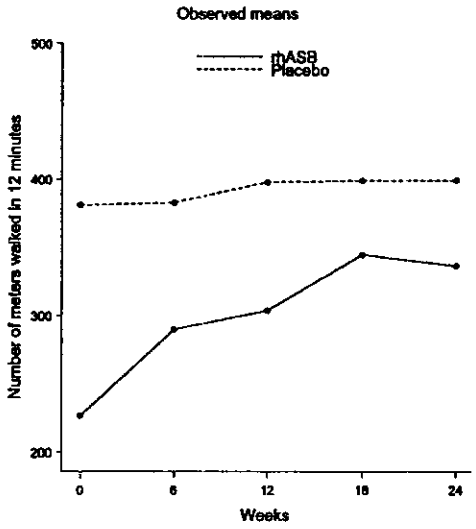
100.0%	maximum	684.95
99.5%		684.95
97.5%		684.95
90.0%		652.58
75.0%	quartile	567.50
50.0%	median	364.50
25.0%	quartile	239.00
10.0%		90.00
2.5%		45.50
0.5%		45.50
0.0%	minimum	45.50

Moments

Mean	381.0125
Std Dev	201.56032
Std Err Mean	45.070258
upper 95% Mean	475.34563
lower 95% Mean	286.67937
N	20

Figure 2. Means of 12 minute walk test over time in the Galsulfase and placebo groups, as observed (a), and adjusted for a hypothetical common baseline (b). Obtained from the applicant's study report, Figure 11-1.

a) Observed



b) Observed, adjusted for baseline

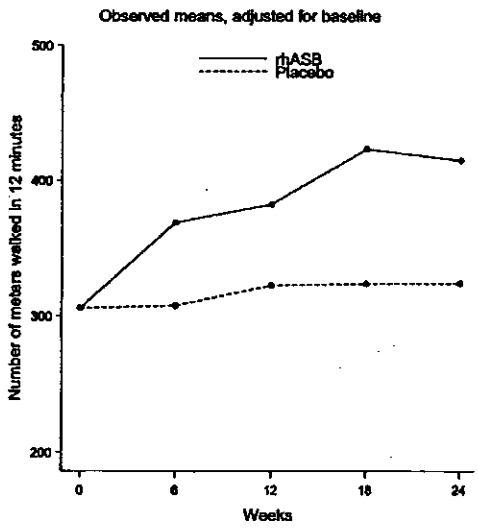


Table 4. Primary efficacy outcome, the results from the 12 minute walk test. Obtained from Table 11-6 in the applicant's study report.

	rhASB			Placebo				
	Baseline	**Week 24**	**Change**	**Baseline**	**Week 24**	**Change**	**Diff. in Changes***	**p-value**
Observed (raw)								
N	19	19	19	20	19	19	—	—
Mean±SD	227±170	336±227	109±154	381±202	399±217	26±122	83±45	—
Median	210	316	48	365	373	34	—	—
%iles (25, 75)	90, 330	125, 483	7, 183	256, 560	204, 573	-3, 89	—	—
Minimum	9	5	-48	46	64	-266	—	—
Maximum	623	797	440	685	747	267	—	—
Fitted (predicted)**								
Mean±SE	—	424 ± 28	—	—	332±27	—	92±40	0.025

* Mean ±SE.

**For fitted means: Week 24 estimate, adjusted for baseline.

Table 5. **Primary efficacy variable, distance walked in 12 minutes: Primary analysis model from BioMarin and two models used by this reviewer for additional sensitivity analyses, using the ITT data set.** The models are described in the part 3.1 of this review.

Model	Statistical comparison Comparison of means, Galsulfase – Placebo at Week 24 Mean (95% CI)	P-value
Model 1, the applicant's primary analysis (also re-expressed as Model 2 by this reviewer)	92 (11, 172)	0.025
Model 3, this reviewer's sensitivity analysis	103 (0, 206)	0.050
Model 4, this reviewer's sensitivity analysis	Comparison of slopes (m/week) Galsulfase 4.7 ± 1.3 Placebo 1.3 ± 1.3	0.054

Table 6. **Summary of sensitivity analyses conducted by the applicant for the primary efficacy variable, 12 minute walk distance.**

Subset of data	Description of analysis (Model 1 is described in section 3.1)	Galsulfase - Placebo (95% CI, p-value) [1]	Reference in application
ITT	Model 1	92 (11, 172), p=0.025	Table 14-62
ITT	Model 1, but excluding site	78 (1, 155), p=0.047	Table 14-62
ITT	Model 1, but with AR(1) in correlation structure	93 (14, 173), p=0.022	Table 14-63
ITT	Model 1, but with UN in correlation structure	82 (-15, 179), p=0.095	Table 14-63
ITT	Model 1, but with Time as linear instead of categorical	94 (17, 171), p=0.017	Table 14-64
ITT, but only using the first replicate of the 12 minute walk test	Model 1	82 (-8, 173), p=0.075	Table 14-65
ITT	Model 1, but excluding the time by treatment interaction	76 (1, 150), p=0.047	Table 14-66
ITT, but including patient 021-066's second measurement	Model 1	79 (-1, 159), p=0.052	Table 14-67
ITT	Model 1, but including additional		Table 14-68

Subset of data	Description of analysis (Model 1 is described in section 3.1)	Galsulfase - Placebo (95% CI, p-value) [1]	Reference in application
	baseline covariates, as follows [2].		
	Age	88 (5, 171), p=0.039	
	Age, gender	85 (7, 162), p=0.033	
	Age, gender, height	67 (-10, 143), p=0.088	
	Age, height	65 (-17, 146), p=0.120	
	Gender	92 (18, 167), p=0.016	
	Gender, height	66 (-10, 142), p=0.087	
	Height	62 (-18, 143), p=0.130	
Walk-Eligible Subset	Model 1	115 (22, 207), p=0.016	Table 14-69
≤ 400 m Subset	Model 1	118 (16, 220), p=0.024	Table 14-70
ITT, but baseline and week 24 data only	ANOVA with treatment, baseline covariate and site	103 (3, 204), p=0.044	Table 14-71
	ANOVA: excluding site	73 (-25, 170), p=0.140	
	t-test on the difference from baseline	85 (-4, 174), p=0.062	
	Wilcoxon test on the difference from baseline, two-group comparison [3]	p=0.290	
Walk-Eligible Subset, baseline and week 24 data only	ANOVA with treatment, baseline covariate and site	124 (1, 246), p=0.048	Table 14-72
	ANOVA: excluding site	86 (-32, 204), p=0.150	
	t-test on the difference from baseline	95 (-13, 203), p=0.082	
	Wilcoxon test on the difference from baseline, two-group comparison [3]	p=0.330	
≤ 400 m Subset	ANOVA with treatment, baseline covariate and site	142 (23, 260), p=0.022	Table 14-73
	ANOVA: excluding site	102 (-20, 223), p=0.096	
	t-test on the difference from baseline	87 (-27, 202), p=0.130	
	Wilcoxon test on the difference from baseline, two-group	p=0.420	

Subset of data	Description of analysis (Model 1 is described in section 3.1)	Galsulfase - Placebo (95% CI, p-value) [1]	Reference in application
	comparison [3]		
ITT	Number of responders[4] Mantel-Haenszel pooled estimate of the odds ratio, stratified by site	Odds ratio, 95% CI, p-value: 2.11 (0.53, 8.5), p=0.30	Table 14.74
Walk-Eligible Subset	Number of responders[4], Mantel-Haenszel test as above.	As above: 2.15 (0.48, 9.7), p=0.32	Table 14.75
≤ 400 m Subset	Number of responders[4], Mantel-Haenszel test as above.	As above: 2.29 (0.50, 10.6), p=0.28	Table 14.76
ITT	Randomization test	one-tailed p = 0.029 [5]	Section 11.4.2.2
ITT, First 6 minutes of 12 MWT	Model 1[6]	52 (14, 90), p=0.007	Table 14.78
ITT, Second 6 minutes of 12 MWT	Model 1	32 (-18, 82), p=0.203	Requested by Dr. Irony

Comments:
1. Some analyses did not provide a confidence interval of "Galsulfase – Placebo" and are so noted in this table.
2. The applicant conducted additional analyses by excluding "site" from the model, but these results are not summarized in this table.
3. The Wilcoxon test does not provide an estimate of difference between the two groups.
4. A responder is a patient with more than an 80 m improvement in walking distance from baseline for the 12 minute walk test.
5. BioMarin concluded that the problems that occurred during the implementation of randomization render the randomization test invalid.
6. The sponsor conducted a more extensive analysis of the first 6 minutes of the 12 MWT, using the full ITT database (summarized in this table), the walk-eligible subset and the ≤ 400 m subset.

Secondary and tertiary efficacy endpoints

Results from the statistical analysis of secondary and tertiary efficacy endpoints were supportive of the conclusion that Galsulfase was superior to the placebo in improving the level of physical endurance in patients with MPS VI. A summary of the key results is as follows:

- The analysis of the 3 minute stair climb results in all randomized patients showed a difference between the mean change in the rates between Galsulfase and placebo of 5.7 ± 2.9 stairs/minute (p=0.053). For the total group, Walk-Eligible subset, and ≤ 400 m subset, the Galsulfase group climbed a mean of approximately 16, 21 and 21 more stairs than the placebo group, with p-values of 0.042, 0.019 and 0.048, respectively.

- Seventeen of 19 Galsulfase patients and no placebo patient had a ≥ 50% reduction in urinary GAG levels between baseline and week 24. The Galsulfase patients had a decrease from a mean (± SD) of 346 ± 128 μg/mg creatinine at baseline to 85 ± 35 μg/mg creatinine at week 24. The placebo patients decreased from 330 ± 114 μg/mg at baseline to 317 ± 80 μg/mg creatinine at week 24. Adjusted for baseline, the analysis of variance showed an estimated mean ± SE difference at week 24 between placebo and Galsulfase of -227 ± 18 μg/mg creatinine ($p<0.001$).

- Patients in both the Galsulfase and placebo groups showed mean improvement for all tertiary efficacy variables. There were no statistically significant differences between the groups except for passive lateral rotation, in which the placebo group had more improvement than the Galsulfase group.

- The Week 24 assessment of pulmonary function for the Galsulfase patients showed small mean improvements over baseline for FET, FEV_1, MVV, FIVC, and FIR, but no change for FVC. The placebo group had an increase for FIVC, mean decreases for FET, FVC, MVV, and FIR, and no change for FEV_1.

Results from 12 minute walk distance from the open label extension study ASB-03-06

Study ASB-03-06 was an open label extension study of patients with MPS VI who were previously treated in study ASB-03-05. Eligible patients began treatment in the extension study during the 25th week but no later than the 26th week with respect to study ASB-03-05. After initiation of study treatment at the local site, patients returned to the primary site for assessments in the 12 minute walk test and the 3 minute stair climb at weeks 36 and 48. Treatment continued as weekly infusions of Galsulfase 1.0 mg/kg administered intravenously over approximately a 4-hour period once a week. Patients and physicians from the ASB-03-05 study entered the ASB-03-06 study blinded, i.e., they did not know what the treatment assignments had been in the ASB-03-05 study.

All 19 patients randomly assigned to the Galsulfase group and the 19 patients randomly assigned to the placebo group who were on study at week 24 in the ASB-03-05 study were enrolled in the ASB-03-06 extension study and completed the 48-week period.

The applicant used a longitudinal analysis of variance model to examine trends over time within each group separately. They used a version of Model 1 (see section 3.1) from study ASB-03-05, excluding terms involving "treatment group." For the analysis of each treatment group, they used data from baseline (week 0) to week 48, encompassing both study ASB-03-05 and ASB-03-06. They evaluated comparisons of the change from week 24 to baseline, the change from week

48 to baseline, and the change from week 48 to week 24. They did not make a statistical comparison between the two groups.

The observed and fitted means for each treatment group by week are depicted in Figure 3. The applicant noted that both groups showed improvement from week 24 to week 48. The estimated mean changes ± SE were 36 ± 25 for the original Galsulfase group and 65 ± 23 for the original placebo group. They also noted that from week 24 onward, the original placebo group evidenced a steady increase in average 12 minute walk distance through week 48. The original Galsulfase group showed a slight improvement over the same time frame. They interpreted these findings as confirmatory with respect to the ability of Galsulfase to improve endurance in MPS VI patients.

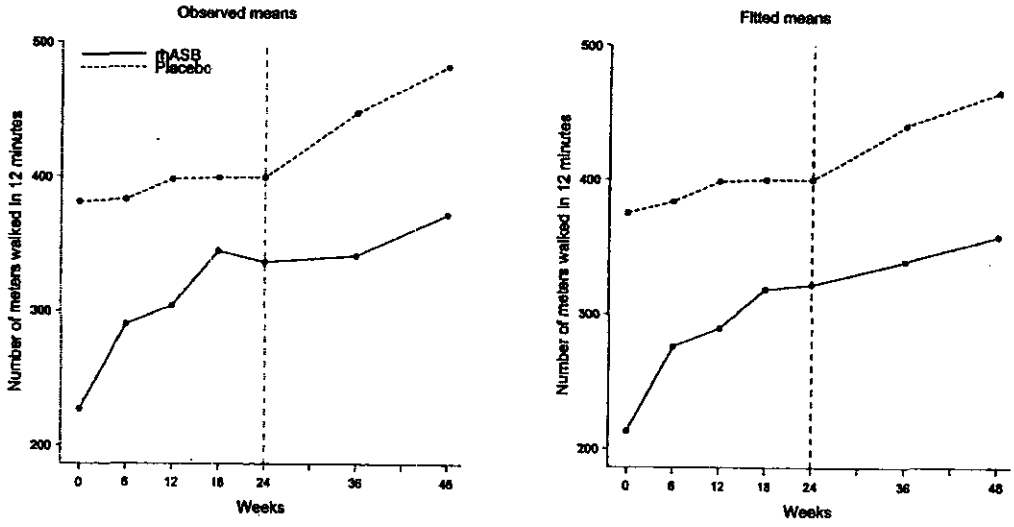
In order to gain additional insight on the open label extension portion of this study, this reviewer extended the "slope" approach used in Model 4 (section 3.1) from the sensitivity analysis of study ASB-03-05. For each subject, the slope of the regression of the 12 minute walk distance on week was obtained for weeks 24 through 48 (Study ASB-03-06). A subject's slope was then compared between the two study periods. If the slope for weeks 24-48 was greater (more positive) than the slope for weeks 0 through 24, this was interpreted as an "improved slope" for the open label extension study. For example, Patient 024-002 had a slope of -2.300 in weeks 0-24 and a slope of 9.583 in weeks 24-48 (Table 7). This patient would be classified as "having an improved slope" because the slope of 9.583 is more positive than the slope of -2.300. Patient 021-001 had a slope of 15.017 in weeks 0-24 and 5.917 in weeks 24-48 (Table 7). This patient would be classified as "not having an improved slope" because the slope of 5.917 is less positive than the slope of 15.017.

In the placebo group, 10 out of 19 (53%) patients had an "improved slope" in the open label extension study compared with the placebo controlled study (Table 7). A somewhat smaller percentage of patients in the Galsulfase group had an "improved slope" (8 out of 19, or 42%; see Table 7). This finding is consistent with the interpretation that patients in the placebo group expressed their potential to improve their 12 minute walk distance after they were switched to Galsulfase. This consistency may strengthen the findings for the primary efficacy variable.

Table 7. 12 minute walk test for each patient, showing the linear regression slopes obtained for weeks 0-24 (Study ASB-03-05) and for weeks 24-48 (Open Label Extension, Study ASB-03-06)

Patient Number	Site	Group	Study ASB-03-05 Slope Wk 0-24	Study ASB-03-06 Slope Wk 24-48	"Improved Slope"? Slope Wk 24-48 > Slope Wk 0-24?
026-002	026	Galsulfase	-0.705	3.556	Yes
026-006	026	Galsulfase	-2.104	1.844	Yes
024-002	024	Galsulfase	-2.300	9.583	Yes
024-003	024	Galsulfase	0.813	2.375	Yes
024-005	024	Galsulfase	2.633	3.979	Yes
020-002	020	Galsulfase	-0.034	0.135	Yes
018-002	018	Galsulfase	2.177	2.885	Yes
018-004	018	Galsulfase	-0.274	0.294	Yes
026-003	026	Galsulfase	4.179	1.690	No
026-005	026	Galsulfase	2.023	-0.906	No
025-001	025	Galsulfase	1.427	0.375	No
025-004	025	Galsulfase	15.575	-0.750	No
024-007	024	Galsulfase	0.283	-2.875	No
021-001	021	Galsulfase	15.017	5.917	No
021-004	021	Galsulfase	7.158	5.792	No
021-006	021	Galsulfase	14.250	4.024	No
020-003	020	Galsulfase	16.316	0.604	No
020-005	020	Galsulfase	0.903	0.613	No
020-007	020	Galsulfase	5.317	-10.219	No
026-001	026	Placebo	-9.020	17.485	Yes
025-005	025	Placebo	-3.125	3.313	Yes
024-004	024	Placebo	1.308	2.333	Yes
021-002	021	Placebo	1.117	1.646	Yes
021-003	021	Placebo	2.475	3.750	Yes
020-001	020	Placebo	-1.203	-0.183	Yes
020-004	020	Placebo	-11.120	13.625	Yes
018-003	018	Placebo	-2.178	2.685	Yes
018-005	018	Placebo	1.984	6.865	Yes
018-006	018	Placebo	1.058	6.081	Yes
026-004	026	Placebo	4.434	-4.075	No
025-002	025	Placebo	3.708	2.625	No
025-003	025	Placebo	10.350	-4.563	No
024-001	024	Placebo	3.458	-0.583	No
024-006	024	Placebo	-0.200	-0.896	No
024-009	024	Placebo	1.017	-0.271	No
021-005	021	Placebo	4.192	2.563	No
020-008	020	Placebo	11.200	-0.313	No
018-001	018	Placebo	1.949	1.029	No
020-006	020	Placebo	---	---	---

Figure 3. **Means of 12 minute walk test over time. Obtained from Figure 8-1 of the application.**



Recommendations for labeling on efficacy results

This reviewer worked with the review team for Galsulfase to develop modifications to the text and tables concerning the results from the 12 minute walk test and the 3 minute stair climb. These modifications, depicted in Tables 8, 10 and 12, simplify the description of the results in the text, and omit the potential for confusion in the tables provided by the applicant (shown in Tables 9 and 11) due to the imbalance between the two groups at baseline in these variables.

Table 8. **Proposed revision to label text concerning results from the 12 minute walk test results and the 3 minute stair climb**

Draft text from proposed label in application 12 minute walk (lines 104-110)

Draft text from proposed label in application 3 minute stair climb (lines 113-117

Proposed replacement text for these sections on the label, developed by the FDA review team for Galsulfase.
The Galsulfase treated group showed greater mean increases compared to the placebo group in the distance walked in 12 minutes (12 minute walk test, 12 MTW) (Table 1) and the rate of stair climbing in a 3 minute stair climb test (Table 2).

Table 9. Proposed table from applicant, summarizing 12 minute walk test results, in proposed labeling (lines 111-112)

Table 10. Recommended table for summarizing 12 minute walk test results in labeling.

	Galsulfase			Placebo			Galsulfase - Placebo
	Baseline	Week 24	Change	Baseline	Week 24	Change	Difference in Changes
N	19	19	19	20	19 [a]	19 [a]	19
Mean± SD	227±170	336±227	109±154	381±202	399±217	26±122	83±45 [b] 92±40 [c] P=0.025
Median	210	316	48	365	373	34	
Percentiles (25^{th}, 75^{th})	90, 30	125, 483	7, 183	256, 560	204, 573	-3, 89	

a One subject in the placebo group dropped out before week 24
b Observed mean of Galsulfase – Placebo ± SE
c Model-based mean of Galsulfase – Placebo ± SE, adjusted for baseline

Table 11. Proposed table from applicant, summarizing 3 minute stair climb results, in proposed labeling (lines 118-119).

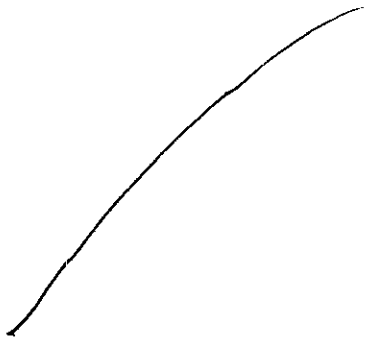


Table 12. Recommended table for summarizing 3 minute stair climb results in labeling.

	Galsulfase			Placebo			Galsulfase - Placebo
	Baseline	Week 24	Change	Baseline	Week 24	Change	Difference in Changes
N	19	19	19	20	19[a]	19[a]	19
Mean± SD	19.4±12.9	26.9±16.8	7.4±9.9	31.0±18.1	32.6±19.6	2.7±6.9	4.7±2.8[b] 5.7±2.9[c] P=0.053
Median	16.7	22.8	5.2	24.7	29.0	4.3	
Percentiles (25^{th}, 75^{th})	10.0, 26.3	14.8, 33.0	2.2, 9.9	18.1, 51.5	14.2, 57.9	1.0, 6.2	

a One subject in the placebo group dropped out before week 24
b Observed mean of Galsulfase – Placebo ± SE
c Model-based mean of Galsulfase – Placebo ± SE, adjusted for baseline

3.2 Evaluation of Safety

The safety of Galsulfase was assessed based on the results of 3 clinical trials, 2 controlled (Study ASB-00-01 and Study ASB-03-05) and 1 open label (Study ASB-01-04). In each study, the following measures were assessed periodically: hematology and chemistry laboratory studies of bone marrow, liver function, kidney function, urinalysis, anti-ASB IgG antibody levels, vital signs, physical examinations, history of MPS VI signs and symptoms, adverse events, concomitant medications, ECGs, echocardiograms, and complement parameters. Investigators were instructed to record all worsening signs, symptoms, or physical findings as adverse events. In addition, all laboratory abnormalities were assessed for clinical significance, and clinically significant abnormalities were reported as adverse events.

All patients receiving any amount of study drug were included in the safety analysis for each study and in the overall analysis. Data were summarized descriptively. All events were coded and listed by system organ class and preferred term based on the Medical Dictionary for Regulatory Activitieis (MeDRA), Version 6.1. Listings were provided for deaths, withdrawals due to adverse events and serious adverse events (SAEs). All adverse events occurring during infusion were recorded and were listed separately. Study drug-related adverse events that occurred during infusion, termed infusion-associated reactions (IARs), were reviewed, and efforts were made to identify those events that could represent elements of an anaphylactoid reaction to study drug. Particular attention was given to events such as urticaria, rash, pruritus, fever, hypotension, edema, throat tightness, dyspnea, and wheezing, as well as events that occurred during multiple infusions.

A total of 56 patients with MPS VI were enrolled and treated in the 3 Galsulfase clinical studies. Twenty patients received placebo during their participation in study ASB-03-05. Study drug exposure for the remaining 36 patients is summarized in Table 13 below:

Table 13. Weeks of Galsulfase exposure by dose Group. Obtained from Table 2 of the applicant's Integrated Safety Report.

Exposure (weeks)	0.2 mg/kg (n = 2)	0.2/1.0 mg/kg (n = 2)[a]	1.0 mg/kg (n = 32)[b]
24	1[c]	2	32
48	0[d]	2	13
72	0	2	13
96	0	2	3
144	0	2	3

[a] Patients 1–014–045 and 1–014–041, Study ASB–00–01, switched from 0.2 mg/kg to 1.0 mg/kg at Weeks 59 and 69, respectively.

[b] Includes 19 patients treated in Study ASB–03–05 for 24 weeks, 10 patients treated in Study ASB–01–04 for 72 weeks, and 3 patients treated in Study ASB–00–01 for 144 weeks.

[c] Patient 1–014–040, Study ASB–00–01, withdrew from study after Week 3.

[d] Patient 1–014–050, Study ASB–00–01, withdrew from study after Week 32.

Compliance with the Galsulfase treatment regimen was high, with few infusions missed overall. Patients in ASB-00-01 and ASB-01-04 have continued to receive study drug. Data for these studies have been collected through 144 weeks and 72 weeks, respectively.

3.2.1 Adverse Events

All 56 patients treated in these 3 studies reported at least 1 adverse event, and 1511 adverse events were reported overall: 1167 for the 36 Galsulfase-treated patients and 344 for the 20 placebo-treated patients. A single death reported, in a patient from study ASB-00-01, who died 20 months after his final study drug infusion. There were no discontinuations due to adverse events. A total of 39 SAEs were reported by 14 patients across all clinical studies, and 33 severe adverse events were reported by 20 patients. Study drug-related adverse events and adverse events occurring during infusion were reported for patients in each treatment group, although they tended to occur more often in patients receiving Galsulfase than in those receiving placebo. IARs (study drug-related adverse events occurring during infusion) were reported for 23 patients. In 8 of these patients, the IARs were considered to be consistent with an anaphylactoid reaction to study drug. Table 14 summarizes the incidence and frequency of adverse events in the 3 clinical studies.

Table 14. **Incidence and frequency of adverse events.** Obtained from Table 5 of the applicant's Integrated Safety Report.

	No. of Patients / No. of Events			
	0.2 mg/kg (n = 2)	0.2/1.0 mg/kg (n = 2)[a]	1.0 mg/kg (n = 32)	Placebo (n = 20)
Any adverse event	2 / 29	2 / 131	32 / 1007	20 / 344
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	7 / 17	4 / 12
Severe adverse events	1 / 2	2 / 2	13 / 20	4 / 9
Study drug–related adverse events	2 / 14	2 / 27	19 / 149	6 / 14
Adverse events during infusion	1 / 11	2 / 29	20 / 166	8 / 13
IARs (study drug-related adverse events during infusion)	1 / 11	2 / 24	16 / 102	4 / 6

Source: Table 14.3.1–4.1

[a] Patients 1–014–045 and 1–014–041, Study ASB–00–01 (CTD Section 5.3.5.1), switched from 0.2 mg/kg to 1.0 mg/kg at Weeks 59 and 69, respectively.

Within these SOC's, the specific adverse events that occurred most commonly (≥ 15% of patients) among patients receiving Galsulfase at any dose (n=36) were headache (19 patients); pyrexia and arthralgia (18 patients each); vomiting (16 patients); upper respiratory infection (URI, 15 patients); abdominal pain (14 patients), diarrhea, ear pain, and cough (13 patients each); otitis media (12 patients); otorrhea (10 patients); chest pain, back pain, nausea and rash (9 patients each); pain in extremity, infusion site pain and pruritus (8 patients each); conjunctivitis, pain, nasal congestion, and poor venous access (7 patients each); and ear infection, pharyngitis, myalgia, and urticaria (6 patients each). The adverse events occurring most commonly among placebo-treated patients (n=20) were headache (12 patients); pyrexia and pain in extremity (8 patients each); vomiting, URI and arthralgia (7 patients each); abdominal pain, diarrhea, and cough (6 patients each); nausea, nasopharyngitis and pneumonia (5 patients each); ear pain, otitis media, sinusitis, back pain, and rhinorrhea (4 patients each); and anemia, fatigue, hernia pain, influenza-like illness, hepatomegaly, neck pain, alopecia, pruritus, restrictive pulmonary disease, and poor venous access (3 patients each).

The most frequent adverse events (> 2.5% of all events) among Galsulfase-treated patients were headache, pyrexia, URI, arthralgia, vomiting, rash, and otorrhea. For placebo-treated patients, the most frequent adverse events were pyrexia, headache, abdominal pain, vomiting, back pain, pain in extremity, cough, and URI. In general, the pattern of most frequent adverse events was

similar for Galsulfase-versus placebo-treated patients; however, rash, otorrhea, and arthralgia were seen more frequently in Galsulfase-treated patients.

Of the 1511 adverse events reported for 56 patients in the 3 clinical trials, a total of 204 adverse events (13.5%) were considered to be related to study drug administration, 190 in Galsulfase-treated patients and 14 in placebo-treated patients. Of the 204 study drug-related events, 143 occurred during infusion and were considered IARs.

Of the 1167 adverse events reported for the 36 Galsulfase-treated patients, 933 (79.9%) were mild, 210 (18.0%) were moderate, and 24 (2.1%) were severe. Severe adverse events observed during infusion for Galsulfase-treated patients included conjunctivitis, chest pain, apnea, dyspnea, obstructive airways disorder, rash/macular rash, and urticaria. Of the 344 adverse events reported for the 20 placebo-treated patients, 235 (68.3%) were mild, 100 (29.1%) were moderate, and 9 (2.6%) were severe. Severe adverse events among placebo-treated patients included abdominal strangulated hernia and sleep apnea syndrome; none of the severe adverse events occurred during infusion.

A total of 39 SAEs (2.6% of all events) were reported overall for the 3 studies: 27 in Galsulfase-treated patients and 12 in placebo-treated patients. Three SAEs were considered to be related to study drug: Two related SAEs, apnea and urticaria, occurred during study drug infusion, both in Galsulfase-treated patients. The third related SAE, asthma, several hours after study drug infusion.

The death that took place during the course of these studies was a patient who died of complications of malignancies after withdrawing from Galsulfase treatment after 3 weeks. The patient was determined to have a germline mutation of the MSH2 gene that was believed to be the underlying cause of the malignancies.

Clinical laboratory evaluations

Changes in chemistry and hematology laboratory parameters were seldom judged to be clinically significant by the investigator, and the majority of the change were judged to be related to underlying MPS VI disease or intercurrent illness. There were few laboratory adverse events reported. Anemia was the most common event reported. A total of 4 episodes of anemia were reported for 3 of 36 Galsulfase-treated patients and 9 episodes were reported for 8 of 19 placebo-treated patients.

Cardiac evaluations

Cardiovascular adverse events were generally well balanced between Galsulfase- and placebo-treated patients. The types of adverse events observed in both groups are consistent with the cardiac manifestations of MPS VI disease.

Vital signs, physical findings, and other observations

Vital sign abnormalities were infrequent in patients receiving Galsulfase infusions. There was no apparent difference in the incidence of clinically significant vital sign abnormalities between patients treated with Galsulfase and patients treated with placebo. No consistent worsening of physical findings for any body system was observed in the 3 clinical trials of Galsulfase. No consistent adverse changes in MPS VI signs and symptoms were seen in patients treated with Galsulfase versus placebo.

Immunogenicity

Of the 36 patients treated with Galsulfase in the 3 clinical trials, 34 patients had evidence of antibody development during the course of their treatment with Galsulfase. Initial evidence of antibody development typically appeared following 4-8 weeks of treatment. Data from patients treated for more than 48 weeks suggested that there may be a development of tolerance (and a decline in antibody levels) in patients over time.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The study patients ranged in age from 5 to 29 years; two-thirds of the patients were female. The racial/ethnic composition (62% white, non-Hispanic, 10% Hispanic, 28% other) was consistent with the demographic distribution of the particular sites enrolling patients. The racial composition of the 2 groups differed somewhat, with 15 of the 19 Galsulfase patients (79%) defined as white and 9 of the 20 placebo patients (45%) so defined. The placebo patients were, on average, younger (mean age placebo: 19.7 hrs; Galsulfase: 13.7 yrs) and lighter than the Galsulfase patients (mean weight placebo: 20.8 kg; Galsulfase 24.6 kg).

Because of the small overall size of the study, additional analyses of subgroups defined by sex, race or age were not included as part of this review.

4.2 Other Special/Subgroup Populations

The applicant based some analyses on the subset of 32 patients who satisfied the eligibility requirements with respect to their screening walk test results (not more than 270 m in 6 minutes or not more than 400 m in 12 minutes). This population is called the "Walk-Eligible Subset." A third set of analyses considered primary and secondary efficacy variables in the subset of patients who walked $\leq$ 400 m in 12 minutes at baseline. This group of 28 patients is termed the "$\leq$ 400

Meter Subset." Results from the analysis of the 12 minute walk distance in these subsets are described in part 3.1.

The applicant also evaluated the influence of individual site on the statistical conclusions about the 12 minute walk test by re-analyzing the data several times, each time excluding a different site. Sites 20 (Germany) and 21 (England) are the most influential to the study conclusions with respect to this analysis, because the p-value for the comparison between Galsulfase and placebo changes from <0.05 to >0.05 when the analysis is done without each of these studies (Table 15).

Table 15. Analysis of 12 minute walk test excluding individual sites, obtained from Table 11-19 in application.

Excluded Site	n		Mean ± SD of 12-minute Walk Distance at Baseline		Base longitudinal model	
	rhASB	Placebo*	rhASB	Placebo	Estimated mean ± SE of difference between rhASB and Placebo	p-value
018	17	16	243±172	365±205	115±45	0.012
020	15	16	238±171	376±205	62±40	0.13
021	16	17	239±180	423±183	65±48	0.18
024	15	16	163±111	359±216	132±52	0.013
025	17	17	235±178	387±194	87±37	0.022
026	15	18	238±189	374±205	94±44	0.037

*Placebo n includes Patient 020-006, except where site 020 is excluded.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

An issue that raised a review concern was the imbalance in the 12 minute walk distance, the primary efficacy variable, between the two treatment groups in the Phase 3 study. In order to ensure that the study provided a reasonable basis for a statistical comparison between Galsulfase and placebo, this reviewer assessed the allocation process as reported by BioMarin. This reviewer concludes that the process was adequate, provided that the BioMarin personnel who assigned the ID codes to eligible patients were not aware of the list that linked the ID code to the treatment assignment.

5.2 Conclusions and Recommendations

Efficacy

Based on an evaluation of the applicant's analysis and an additional sensitivity analysis, this reviewer concludes that the results for the primary efficacy endpoint were reasonably robust to different approaches to the statistical analysis. The results from the statistical analysis support the conclusion that Galsulfase is superior to the placebo with respect to the average improvement in 12 minute walk distance between week 24 and baseline (Table 5).

This reviewer concludes that the applicant made reasonable decisions concerning the Intention-To-Treat (ITT) data set, the methods used to impute or otherwise allow for missing data or mis-timed data, and the selection of subsets of the data for additional analysis.

Results from the statistical analysis of secondary and tertiary efficacy endpoints were supportive of the overall conclusion that Galsulfase was superior to the placebo in improving the level of physical endurance in patients with MPS VI. Results from the open label extension of study ASB-03-05 were also consistent with the interpretation that the placebo patients were able to improve their 12 minute walk distance after they were switched to Galsulfase.

This reviewer provided recommendations for revising the draft labeling text and tables concerning the results of the 12 minute walk test and the 3 minute stair climb. These recommendations are summarized in Tables 8, 10 and 12 of this review.

Safety

With respect to safety, the applicant has included a warning about infusion reactions in the draft labeling text, and a description of adverse reactions. These appear to be appropriate from a statistical perspective, given the findings on adverse events and infusion-associated reactions.

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