CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125460Orig1s000

MEDICAL REVIEW(S)

OOPD Consult Memo

Date:	January 14, 2014
To:	Elizabeth Ford, RPM, ODE3, DGIEP
From:	John D. Milto, M.D., Medical Officer Office of Orphan Products Development 01/14/14
Through:	Henry Startzman III, M.D., Director, Orphan Drug Designation Program 1/14/2014 Gayatri Rao, M.D., J.D., Director Office of Orphan Products Development GR 1/14/14
Subject:	Medical Officer Consultation: OOPD review of prevalence data to determine whether BMN110 qualifies as a drug for a "rare pediatric disease," as defined in section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(21 U.S.C. 360ff(a)(3)).
Application:	Rare Pediatric Disease Voucher
Applicant/Sponsor:	BioMarin Pharmaceuticals Inc.
Proposed Indication:	Treatment of Muccopolysaccharidosis type IV A (MPS IVA; Morquio A Syndrome)
Date of Request:	January 13, 2014
Materials Reviewed:	Consultation Request and Sponsor supplied summary of prevalence data for MPS IVA

Background:

Reference is made to BioMarin Pharmaceutical Inc. (BioMarin)'s Biologics License Application (BLA), STN 125460/0 submitted on March 29, 2013, for BMN 110 (recombinant human N-acetylgalactosamine-6-sulfatase) for the treatment of patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome).

As a follow up to a discussion held on December 3, 2013 between BioMarin and Dr. Gayatri Rao, Office of Orphan Products Development (OOPD), OOPD, on January 7, 2014, BioMarin is submitting the Pediatric Voucher Request for Vimizim (elosulfase alfa) for the treatment of Mucopolysaccharidosis IVA (Morquio A Syndrome).

The Division of Gastroenterology and Inborn Errors Products requests assistance from OOPD to determine whether BMN110 qualifies as a drug for a "rare pediatric disease," as defined in section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(21 U.S.C. 360ff(a)(3)).

Recombinant human N-acetylgalactosamine-6-sulfatase (elosulfase alfa) was granted orphan drug designation for the treatment of Mucopolysaccharidosis IVA (Morquio A Syndrome) on May 15, 2009.

OOPD Review: The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 defines a rare pediatric disease as 1) a disease that primarily affects individuals aged from birth to 18 years including neonates, infants, children and adolescents; and 2) the disease is a rare disease or condition (affecting fewer than 200,000 persons in the United States).

The sponsor estimates that no more than 800 persons in the United States who have been diagnosed with Morquio A syndrome. To calculate this estimate, the sponsor applies an incident rate of 1/200,000 to 4 million annual births in the U.S. and multiplies this by an assumed life expectancy of 40 years (1/200,000 X 4,000,000 X 40).

Reviewer's Comments:
The Office of Orphan Products Development (OOPD) has accepted a target population estimate of 1,532 for this application in the past (see Orphan-Drug Designation #09-2808). OOPD accepts that the prevalence of Morquio A syndrome in the United States is less than 200,000.

The sponsor cites data from the International Morquio Organization registry program, an ongoing natural history study being conducted by the sponsor and a phase III study being conducted by the sponsor. The sponsor reports that 64-80% of the patients enrolled in these programs are ≤18 years of age (see Appendix A excerpted from the application).

Reviewer's Comments:
The onset of Mucopolysaccharidosis IVA (Morquio A Syndrome) is between 1 and 3 years of age, and afflicted persons rarely live past their mid-thirties[1]. Severely affected individuals only survive into late childhood or adolescence, while less severely affected persons can live into adulthood albeit with a shortened life expectancy[2]. Montaño et al. found that 68% of persons with Morquio A, in an international registry, had a severe phenotype[3]. Based on this percentage of severe phenotype patients and given the severely limited life expectancy of the severely affected Morquio A patient one would expect that no more than 32% of Morquio A patients would survive beyond 18 years of age. Thus the majority of Mucopolysaccharidosis IVA (Morquio A Syndrome) patients would be younger than 18 years of age which meets the FDASIA definition of a a rare pediatric disease. The information provided by the sponsor based on registry and clinical trial enrollment data is supportive.

References

1. http://www.ninds.nih.gov/disorders/mucopolysaccharidoses/detail_mucopolysaccharidoses.htm.

2. http://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-iv.

3. Montaño, A.M., et al. International Morquio A registry: clinical manifestation and natural course of Morquio A disease. *Journal of Inherited Metabolic Disease* 2007;30(2):165-174.

Appendix A

Table 2: Baseline Age of MPS IVA Population in MorCAP

Age Range	
Number of patients - N (%)	325
0–4 years	45 (13.8%)
5–11 years	127 (39.1%)
12–18 years	84 (25.8%)
> 18 years	69 (21.2%)
Years of age	
mean	14.5
median	11.6
min, max	1.1, 65.6

Table 3: Baseline Age in MOR-004 (Intent-to-Treat Population)

	Placebo (n = 59)	**BMN 110 2.0 mg/kg/qow[a] (n = 59)**	**BMN 110 2.0 mg/kg/week (n = 58)**
Age at Enrollment (years)			
n	59	59	58
Mean (SD)	15.0 (11.30)	15.3 (10.79)	13.1 (8.10)
Median	11.9	12.0	11.1
Min , Max	5 , 57	5 , 49	5 , 42
Age Group (years)[b]			
5 - 11	30 (50.8%)	31 (52.5%)	32 (55.2%)
12 - 18	15 (25.4%)	16 (27.1%)	16 (27.6%)
≥ 19	14 (23.7%)	12 (20.3%)	10 (17.2%)

[a] qow, every other week. SD, standard deviation. [b] Stratification Factor.

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/s/

JAMES D BONA
01/15/2014

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS MEDICAL OFFICER CONSULTATION-NOT YET APPROVED

Date:	December 4, 2013
To:	Tamara Johnson, M.D., Medical Reviewer, DGIEP Jessica Lee, M.D., Medical Team Leader, DGIEP
From:	Tracy Kruzick, M.D. M.P.H., Medical Reviewer, DPARP
Through:	Banu Karimi-Shah, M.D., Medical Team Leader, DPARP
Through:	Lydia Gilbert-McClain, M.D., Deputy Division Director, DPARP
Subject:	Anaphylaxis and hypersensitivity labeling for Elosulfase alfa (Vimzim)

General Information

BLA/IND#:	BLA 125460
Sponsor:	Biomarin Pharmaceutical, Inc.
Drug Product:	Elosulfase alfa (Vimizim ™)
Request From:	Elizabeth Ford, Regulatory Project Manager, DGIEP
Date of Request:	July 25, 2013
Date Received:	July 25, 2013
Materials Reviewed:	Consult request form; IR case narratives from the Integrated Summary of Safety Listings 1.19.2 and 1.19.3; Product label

I. Executive Summary

This is a Medical Officer response to a request for consultation from the Division of Gastroenterology and Inborn Errors Products (DGIEP) to assist in the analysis of anaphylaxis and hypersensitivity occurring in the clinical development program for elosulfase alfa. Elosulfase alfa is a new hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme replacement therapy indicated for patients with mucoplysaccharidosis type IVA, also known as Morquio A syndrome, submitted under BLA 125,460. Mucopolysaccharidosis IV is an autosomal recessive mucopolysaccharide storage disease. The proposed dosing regimen is 2 mg/kg given as an intravenous infusion over 4 hours, administered every other week. Pre-treatment with antihistamines with or without antipyretics is recommended 30-60 minutes prior to the start of the infusion.

As a part of the consultation, DGIEP is seeking our guidance/recommendations for the Boxed Warning and the Warnings and Precautions sections of the product label, with respect to the language regarding anaphylaxis and other hypersensitivity reactions, as the Sponsor has called many of these (b) (4) As we have recommended in prior consultations to DGIEP for different products, and per the Immunogenicity Draft Guidance, therapeutic proteins may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions that have often been grouped as (b) (4) in the past. Although the term implies a certain temporal relationship, (b) (4) are otherwise not well-defined and may encompass a wide range of clinical events,

including anaphylaxis. In the absence of an agreed upon definition for [redacted] (b) (4) the categorization of certain adverse events as [redacted] (b) (4) is problematic. Specifically, we have recommended that anaphylaxis and hypersensitivity events be separated out as distinct events if possible.

In order to analyze the adverse events temporally related to infusion, and harmonize the Sponsor's labeling with the above rationale, case narratives were requested for each of the patients with hypersensitivity reactions (listings in Modules 1.19.2 and 1.19.3) as identified by the MedDRA SMQs of Angioedema and Anaphylactic Reactions, as preliminary review suggested some of these patients may have experienced anaphylaxis. In addition, the Agency asked that the Sponsor use the 2006 NIAID/FAAN criteria to identify anaphylaxis events.

Initially, DPARP identified 2 more cases of anaphylaxis than the Sponsor. However, after additional communication and clarification, the Sponsor accepted the Agency's evaluation. Of the 235 patients in the safety database for this BLA, 18 patients (7.7%) were identified as having had 26 separate events of anaphylaxis using 2006 NIAID/FAAN criteria. In addition, 26 patients experienced hypersensitivity reactions (urticaria, angioedema, flushing, pruritis, rash, and local hypersensitivity of the nose and ears). In total, 44 patients experienced hypersensitivity reactions, including anaphylaxis.

During the review period, the Sponsor submitted revised labeling in compliance with our recommendation of eliminating the term [redacted] (b) (4) We have used this revised labeling to make some additional edits, as outlined below. Details of the cases and the methodology of DPARP's analysis of these cases follow in Section III.

II. Questions from DGIEP

DGIEP seeks your advice regarding appropriate labeling language, as well as harmonizing the applicant-proposed adverse event categories of [redacted] (b) (4) and "hypersensitivity."

A. DPARP Labeling Recommendations

The Boxed Warning and Warnings and Precautions Section of the most recent and revised version of the Sponsor's product label are provided below, with our edits included as tracked changes. The edits have been entered into the DGIEP e-room.

BOXED WARNING

The boxed warning as proposed by the Sponsor and with additional edits as proposed by DGIEP (also included here) is acceptable, and appears below:

> Life-threatening anaphylactic reactions have occurred in some patients during Vimizim infusions. Anaphylaxis, presenting as cough, erythema, throat tightness, urticaria, flushing, [redacted] (b) (4) -cyanosis, hypotension, rash, dyspnea, chest discomfort, [redacted] (b) (4) and gastrointestinal symptoms [redacted] (b) (4) in conjunction with urticaria have been reported to occur during [redacted] (b) (4) infusions, regardless of duration of the course of treatment. Closely observe patients during and after Vimizim administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring [redacted] (b) (4) *(5.1, 5.2)* [redacted] (b) (4) *(6)]*.

WARNINGS AND PRECAUTIONS

Anaphylaxis and hypersensitivity reactions have been reported in patients treated with Vimizim. In premarketing clinical trials, 18 of 235 (7.7%) patients treated with Vimizim experienced signs and symptoms consistent with anaphylaxis (b) (4) These 18 patients experienced 26 anaphylactic reactions during (b) (4) -infusions (b) (4) -with signs and symptoms including cough, erythema, throat tightness, urticaria, flushing, (b) (4) cyanosis, hypotension, rash, dyspnea, chest discomfort, (b) (4) -and gastrointestinal symptoms (e.g., nausea, abdominal pain, retching, and vomiting) in conjunction with urticaria. (b) (4) These cases of anaphylaxis occurred as early as 30 minutes from the start of infusion and up to three hours after infusion. Anaphylaxis occurred as late into treatment as the 47th infusion.

In clinical trials with Vimizim, 44 (b) (4) /235 (18.7 (b) (4) %) patients experienced hypersensitivity reactions, including anaphylaxis. Hypersensitivity reactions have occurred as early as 30 minutes after infusion but as late as six days after infusion. Frequent symptoms of hypersensitivity reactions (occurring in more than 2 patients) included anaphylactic reactions, urticaria, (b) (4) peripheral edema, cough, dyspnea, and flushing.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when Vimizim is administered. Observe patients closely for an appropriate period of time after administration of Vimizim, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur.

Because of the potential for hypersensitivity reactions, administer antihistamines with or without antipyretics prior to infusion (b) (4) - Management of hypersensitivity reactions should be based on the severity of the reaction and include slowing or temporary interruption of the infusion and/or administration of additional antihistamines, antipyretics, and/or corticosteroids for mild reactions. However, if severe hypersensitivity reactions occur, immediately stop the infusion of Vimizim and initiate appropriate treatment.

Consider (b) (4) the risks and benefits of re-administering Vimizim following a severe reaction. (b) (4)

III. Background and Methodology

A. DPARP Approach to Anaphylaxis

Although anaphylaxis has widely been regarded as a severe, potentially fatal, systemic allergic reaction that occurs after contact with an allergy-causing substance, there has been no universal agreement on the clinical definition of anaphylaxis or the criteria for diagnosis. Because the lack of specific diagnostic criteria hampered research, created confusion among health care providers, and led to inconsistent diagnosis and treatment of patients, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened meetings in 2004 and 2005 to address this need. The symposia involved over 18 physician, patient advocate, regulatory, and scientific organizations including the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; the Centers for Disease

Control and Prevention; the Food Allergy Initiative; the US Food and Drug Administration; the European Academy of Allergy and Clinical Immunology; and the Australasian Society of Clinical Immunology and Allergy. The symposia defined anaphylaxis as a clinical syndrome characterized by acute onset of illness with involvement of skin, mucosal tissue and respiratory and/or cardiovascular systems.[1] It is worth noting that the NIAID/FAAN diagnostic criteria do not grade the severity of anaphylaxis. By virtue of multi-organ, multi-system involvement and the unpredictable nature of anaphylaxis, all anaphylactic reactions are considered severe and potentially life-threatening.

The three recommended NIAID/FAAN diagnostic criteria are as follows:

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula), and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a ***<u>likely</u>*** allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to ***<u>known</u>*** allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Since their inception, DPARP has used the NIAID/FAAN criteria to identify cases consistent with anaphylaxis. For the evaluation of new molecular entities, DPARP typically approaches the determination of anaphylaxis by limiting the identification to cases fulfilling criterion #1 above, in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. However, as several subjects were exposed to Elosulfase before having a reaction that qualified per criteria #2 above, these cases were counted since prior exposure would qualify elosulfase as a "likely allergen".

B. Anaphylaxis Cases in the Elosulfase Alfa Clinical Development Program

The Sponsor used the SMQs of Anaphylactic Reaction and Angioedema to identify hypersensitivity events in their clinical trial safety database. Using these search criteria, the Sponsor identified 73 patients, of which they reported 16 patients to have met NIAID/FAAN criteria for anaphylaxis. DPARP's analysis was notable for the following:

- 18 subjects (the Sponsor initially identified 16) experienced anaphylaxis
- 26 separate events of anaphylaxis (the Sponsor initially identified 24) occurred
- 26 subjects experienced hypersensitivity reactions (urticaria, angioedema, flushing, pruritis, rash, and local hypersensitivity of the nose and ears; Appendix 1)
- 62 separate events of hypersensitivity occurred (not including anaphylaxis; Appendix 1)
- 44 subjects experienced hypersensitivity reactions, including anaphylaxis

1. Anaphylaxis Cases

Subject:	**Events coded as:**
MOR002-0119-2007	Type I hypersensitivity
MOR004-0020-4141	Hypersensitivity
MOR004-0021-4005	Anaphylaxis
MOR004-0021-4103	Cough, erythema
MOR004-0050-4063	Throat tightness
MOR004-0109-4025	Urticaria
MOR004-0109-4025	Urticaria
MOR004-0109-4028	Cough, flushing, erythematous rash
MOR004-0111-4019	Cyanosis, hypotension
MOR004-0121-4139	Urticaria
MOR004-1075-4007	Anaphylactic reaction
MOR004-1075-4007	Anaphylactic reaction
MOR004-1159-4109	Cough, rash, dyspnea
MOR004-1159-4117	Urticaria, hypotension
MOR004-1159-4117	Anaphylactic reaction, allergic reaction
MOR004-1167-4068	Urticaria, chest discomfort
MOR007-0018-7005	Urticaria
MOR007-0018-7005	Urticaria
MOR008-0109-8106	Urticaria
MOR002-0121-2003	Generalized rash
MOR002-0121-2003	Infusion related reaction

MOR002-0121-2003	Drug eruption
MOR002-0121-2003	Infusion related reaction
MOR002-0121-2003	Infusion related reaction
MOR004-1017-4016	Mild dyspnea, mild flushing
MOR004-1075-4050	Mild cough, mild flushing

2. Indeterminate Cases of Anaphylaxis

For several of the narratives, full clinical information was not available, and so the determination of anaphylaxis was difficult. While these are not included in the final frequency calculation due to lack of information, a brief discussion of these cases is as follows. For full case narratives, refer to Appendix 3**.**

Subject No: MOR004-0050-4063 (9-year-old White female)
Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004) Premedication(s): Ranitidine, acetaminophen, diphenhydramine Timing: During 16th infusion (45 minutes after start of infusion)

This subject experienced anaphylaxis on February 24, 2012. The infusion on February 29th should have been counted as a separate event (it was counted as part of event #1). On February 29th, the subject experienced both skin involvement (itching) and abdominal pain. It is not described how long the abdominal pain persisted; if it was persistent, this event would fulfill criteria 2 of the NIAID/FAAN criteria for anaphylaxis.

Subject No: MOR004-0021-4005 (5-year-old White female)
Event #5:
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005) Premedication(s): Acetaminophen, chlorphenamine, ranitidine, prednisolone, montelukast
Timing: During 19th infusion in MOR-005 (approximately 3 hours after start of infusion)

This subject experienced skin involvement (uritcaria) as well as nausea. If the nausea was persistent, then this would fulfill criteria 2 of the NIAID/FAAN criteria for anaphylaxis.

Subject No: MOR002-0021-2014 (7-year-old White female)

Treatment Arm: BMN 110 1.0 mg/kg/week (MOR-002 Continuation Period) Premedication(s): Acetaminophen, cetirizine
Timing: Day of the 47th infusion (timing not reported)

This subject experienced wheezing at unknown time on the day of infusion. Wheezing during infusion would be highly suspicious for anaphylaxis; if more information were available (timing, vital signs, documentation of presence/absence of skin findings) this may have been classified as anaphylaxis.

Subject No: MOR004-0020-4140 (6-year-old White male)

Treatment Arm: BMN 110 2.0 mg/kg/qow (MOR-004) Premedication(s): Cetirizine
Timing: During 6th infusion (75 minutes after start of infusion)

This subject experienced a "non-serious moderate systemic reaction." However, the reaction was severe enough to cause cessation of the infusion, and IV fluids were administered. In addition, despite administration of IV fluids, blood pressure still dropped.

Subject No: MOR004-0020-4145 (13-year-old White female)
Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/qow (MOR-004) Premedication(s): Cetirizine
Timing: During 7th infusion (2.25 hours after start of infusion)

This subject experienced a "non-serious moderate allergic reaction". However, the reaction was severe enough for the infusion to stop and IVF plus epinephrine to be administered. In addition, blood pressure dropped despite IV fluid administration.

Subject No: MOR004-1073-4097 (12-year-old White male)
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005) Premedication(s): Chlorphenamine
Timing: During 13th infusion in MOR-005 (20 minutes after start of infusion)

This case is concerning for anaphylaxis: the subject experienced wheezing, cyanosis, cough, and pallor. The reaction was serious enough to stop the infusion. In addition, blood pressure dropped.

Subject No: MOR007-0021-7009 (3-year-old Asian male) Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Acetaminophen, chlorphenamine, prednisolone
Timing: During the 24th infusion (3.25 hours after the start of the infusion)

This patient experienced a "non-serious grade 2 hypersensitivity reaction". However, the reaction was severe enough to stop the infusion so is concerning for potential anaphylaxis.

Subject No: MOR007-0021-7013 (4-year-old White female)
Treatment Arm: BMN 110 2.0 mg/kg/week Premedication(s): Ranitidine, cetirizine, acetaminophen
Timing: 1 hour after the 18th infusion

This subject experienced skin involvement (urticaria), "distress", and hospitalization. It is being assumed that this was psychological distress, not respiratory distress; the latter would cause this case to be classified as anaphylaxis.

Subject No: MOR007-1073-7011 (4-year-old White male) Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Chlorphenamine
Timing: Day of the 14th infusion (timing not specified)

This patient experienced wheezing on the day of infusion without a specified time. Wheezing during infusion would be highly suspicious for anaphylaxis; if more information were available (timing, vital signs, documentation of presence/absence of skin findings) this may have been classified as anaphylaxis.

IV. Appendices

A. Appendix 1: Hypersensitivity cases; for full case narratives, please see IR response.

MOR004-0021-4005 (urticaria; events 6, 7)
MOR004-0109-4028 (urticaria; events 2, 3)
MOR004-0111-4019 (flushing; event 1)
MOR004-1159-4117 (urticaria; events 1, 2)
MOR004-1167-4068 (urticaria; event 2)
MOR007-0018-7005 (uritcaria; event 3, 4)
MOR008-0109-8106 (urticaria; event 2)
MOR 004-1159-4118 (uritcaria; events 1-4)
MOR004-0050-4049 (rash, pruritis; event 2)
MOR004-0109-4028 (urticaria; events 2, 3)
MOR004-0021-4002 (lip swelling)
MOR002-0121-2012 (edema, urticaria; events 1-6)
MOR004-0020-4164 (local hypersensitivity of nose and ears; event 1, 2)
MOR004-0021-4129 (lip swelling)
MOR004-0025-4014 (urticaria; events1-15)
MOR004-1073-4044 (uritcaria)
MOR004-1073-4055 (urticaria)
MOR004-1159-4105 (urticaria)
MOR004-1159-4109 (urticaria; events1-4)
MOR004-1073-4115 (urticaria; events 1-4)
MOR004-1075-4006 (urticaria)
MOR004-1235-4094 (urticaria; events1-3)
MOR004-1260-4119 (urticaria)
MOR004-1017-4098 (urticaria)
MOR004-1073-4131 (urticaria)
MOR007-1073-7011 (urticaria; event 2)

B. Appendix 2: Additional cases identified as anaphylaxis.

These cases were not additionally identified by the Sponsor as anaphylaxis but were subsequently agreed upon.

Subject No: MOR004-1017-4016 (7-year-old White female)

Treatment Arm: BMN 110 2.0 mg/kg/qow
Premedication(s): Cetirizine, acetaminophen
Timing: During 15th infusion (40 minutes following start of infusion) Adverse Event(s) and grade: Mild dyspnea, mild flushing

Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/qow) on 25 July 2011. She missed her Week 8 and 9 infusions after being diagnosed with mononucleosis, but otherwise completed all infusions without any reported infusion-related or anaphylactic reactions.
On 11 November 2011, she received premedication with cetirizine and acetaminophen prior to her 15th study infusion. Her pre-infusion vital signs taken at 9:00 AM included pulse 107 beats per minute (bpm), blood pressure 115/56, temperature 36.8°C, and respiratory rate 23/minute. The infusion was started at 9:20 AM at 6 ml/hr, increased to 12 ml/hr at 9:35 AM, and to 24 ml/hr at 9:50 AM.

At 10:00 AM, the subject experienced non-serious mild events of dyspnea and flushing. The infusion rate was decreased to 12 ml/hr. Treatment for the events included acetaminophen. Her vital signs for the next 45 minutes were as follows:

Time	**Pulse (bpm)**	**BP (mmHg)**	**Temperature (°C)**	**Respiratory rate (breaths/minute)**
10:05 AM	119	118/70	36.5	26
10:10 AM	127	100/67	36.5	23
10:20 AM	127	98/58	36.5	23
10:30 AM	121	99/65	36.5	23
10:35 AM	120	98/60	36.6	22

The events of dyspnea and flushing were considered resolved as of 10:20 AM. At 10:45 AM, the infusion rate was increased back to 24 ml/hr. The infusion proceeded as scheduled without a recurrence of symptoms and was completed later that day. The next scheduled infusion was administered on 21 November 2011; no new premedications were given, and the infusion was completed without any infusion-related reactions.

On 28 November 2011, the subject experienced non-serious mild infusion site pain during her scheduled infusion. The IV site was changed, and no other treatment was given. The event resolved, and the infusion was completed without further symptoms. The subject completed the remainder of the infusions in MOR-004 without recurrence of infusion-associated or anaphylactic adverse events.

Subject No: MOR004-1075-4050 (5-year-old White male)

Event 1:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004) Premedication(s): Clemastine, acetaminophen
Timing: During 11th infusion (timing not clear in relation to start of infusion) Adverse Event(s) and grade: Mild cough, mild flushing
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 14 October 2011. On23 December 2011, he received premedication with clemastine and acetaminophen prior to his 11th study infusion. His pre-infusion vital signs taken at 9:20 AM included pulse 116 bpm, blood pressure 111/69,

temperature 36.9°C, and respiratory rate 22/minute, the infusion was started at 9:22 AM at 3 ml/hr and gradually increased to 36 ml/hr by 10:53AM.

At an unreported time on this date, the subject experienced non-serious, mild events of cough and cheek flushing. No treatment was given for the events, and no changes were made to the study treatment infusion. The infusion was completed as scheduled at 1:24 PM.

The flushing resolved at an unreported time later that day, while no stop date was reported for the cough. No change was made to premedications for the next infusion, which was completed as scheduled on 30 December 2011 without recurrence of symptoms.

C. Appendix 3: Indeterminate cases of anaphylaxis.

Subject No: MOR004-0050-4063 (9-year-old White female)
Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004) Premedication(s): Ranitidine, acetaminophen, diphenhydramine Timing: During 16th infusion (45 minutes after start of infusion)
Adverse Event(s) and grade: Moderate throat tightness
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 7 November 2011. On 24 February 2012, the subject received her 16th infusion with BMN 110, following premedication with ranitidine, acetaminophen, and diphenhydramine. The pre-infusion vital signs taken at 9:30 AM included pulse 92 bpm, blood pressure 94/54, temperature 36.6°C, and respiratory rate 28/minute. The infusion was started at 3 ml/hr at 9:35 AM, and gradually increased to 12 ml/hr by 10:05 AM.

At 10:05 AM, the subject developed a mild dry throat and dry mouth, and was offered some water. At 10:20 AM, she developed non-serious moderate throat closing, as well as mild nausea and shivering. The infusion was stopped, and treatment for the events included IV diphenhydramine. Vital signs at 10:35 AM included pulse 89 bpm, blood pressure 113/58, temperature 36.6°C, and respiratory rate 30/minute. The infusion was restarted at 12 ml/hr at 10:35, and gradually increased to 36 ml/hr by 11:35 AM. The events of throat tightness, nausea, shivering, dry throat, and dry mouth were considered resolved at that point.
The infusion was completed by 1:40 PM. Vital signs remained stable for the remainder of the infusion.

No change was made in the premedications for the next infusion (29 February 2012). That infusion was started at 9:25 AM; at 9:50 AM, the subject developed non-serious abdominal pain and irritability, followed by dry throat, itching, shivering, and bilateral extremity muscle twitching over the next 90 minutes; the throat tightness did not recur. Treatment for these events included IV diphenhydramine, hydrocortisone, and ranitidine. The infusion was not interrupted, nor was the dose reduced, in response to the events; the events were considered resolved by 11:40 AM, and the infusion was completed at 2:15 PM. Vital signs remained stable throughout the infusion.

Hydrocortisone was added as a premedication for the next infusion (9 March 2012).
The subject continued to experience similar non-serious symptoms, including irritability, abdominal pain, dizziness, cough, dry throat/mouth, and nausea, through the infusion on

23 April 2012. The events were generally mild and resolved on the same day with similar treatments. Each infusion was completed without being interrupted. The throat tightness did not recur in any infusion.

The investigator considered the event of throat tightness to be possibly related to study treatment.

Subject No: MOR004-0021-4005 (5-year-old White female)
Event #5:
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005) Premedication(s): Acetaminophen, chlorphenamine, ranitidine, prednisolone, montelukast
Timing: During 19th infusion in MOR-005 (approximately 3 hours after start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 27 January 2012, she received her 19th infusion in MOR-005, following premedication with acetaminophen, chlorphenamine, prednisolone, montelukast, and ranitidine. Her pre-infusion vital signs taken at 8:08 AM included pulse 124 bpm, blood pressure 105/64, temperature 37.6°C, and respiratory rate 32/minute. The infusion was started at 1.5 ml/hr at 9:24 AM, then increased gradually to 18 ml/hr by 10:03 AM. At that point, the subject complained of nausea, so the infusion rate was temporarily decreased to 9.0 ml/hr for approximately 15 minutes, before being increased again. By 11:27 AM, the infusion rate was 30 ml/hr. Vital signs taken at that time included pulse 122 bpm, blood pressure 127/69, temperature 37.2°C, and respiratory rate 28/minute.

When the infusion was increased to 30 ml/hr, the subject complained of non-serious grade 1 urticaria. The infusion rate was lowered to 15 ml/hr, and treatment for the event included acetaminophen and chlorphenamine. Vital signs taken at 12:36 PM included pulse 129 bpm, blood pressure 129/76, temperature 37.3°C, and respiratory rate 29/minute. The event persisted, and at 3:05 PM the infusion rate was lowered again, to 7.5 ml/hr. After 20 minutes, it was increased back to 15 ml/hr, and the infusion was completed at 4:29 PM.

The event of urticaria was considered resolved as of 5:25 PM. The subject received her next scheduled infusion on 3 February 2012 without recurrence of the urticaria, and the infusion was completed without dose interruptions or rate changes.

Prednisolone was discontinued as a premedication on 20 July 2012.

Subject No: MOR002-0021-2014 (7-year-old White female)

Treatment Arm: BMN 110 1.0 mg/kg/week (MOR-002 Continuation Period) Premedication(s): Acetaminophen, cetirizine
Timing: Day of the 47th infusion (timing not reported) Adverse Event(s) and grade: Grade 1 wheezing
Serious AE(s): No

This subject started treatment in MOR-002 (0.1 mg/kg/week) on 6 July 2009, and completed the Dose Escalation phase on 10 March 2010. On 14 June 2010, the subject received 1.0 mg/kg of BMN 110 following premedication with acetaminophen and cetirizine. This was her 47th study treatment infusion, and her 13th infusion at 1.0 mg/kg in the Continuation Period. No adverse events were reported during the infusion, and it was completed as scheduled without dose interruptions or rate changes.

On the date of the infusion, the subject experienced non-serious grade 1 wheezing; the timing in relation to the infusion was not reported. Treatment for the event included inhaled salbutamol, and the event was considered resolved as of 28 June 2010. No action was taken with study medication in relation to the event.

The investigator considered the event of wheezing to be not related to study treatment.

Subject No: MOR004-0020-4140 (6-year-old White male)

Treatment Arm: BMN 110 2.0 mg/kg/qow (MOR-004) Premedication(s): Cetirizine
Timing: During 6th infusion (75 minutes after start of infusion) Adverse Event(s) and grade: Moderate hypersensitivity
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/qow) on 28 February 2012. On 3 April 2012, the subject received his 6th infusion with BMN 110 (2.0 mg/kg/qow), following premedication with cetirizine. His pre-infusion vital signs taken at 9:45 AM included pulse 115 bpm, blood pressure 93/67 mmHg, temperature 36.5°C, and respiratory rate 24/minute. The infusion started at 10:10 AM at 3 ml/hr, and gradually increased to 24 ml/hr by 11:10 AM.

At 11:25 AM, the subject developed a non-serious moderate systemic allergic reaction (symptoms not specified). The infusion was temporarily interrupted, and treatment for the event included IV fluids, prednisolone, dimethindene, and ranitidine. The event resolved after about 15 minutes, and the infusion was restarted at a lower rate (12 ml/hr). Vital signs at 12:20 PM included pulse 97 bpm, blood pressure 85/61 mmHg, and temperature 36.9°C. The rate was gradually increased again, and the infusion was completed later that day.

For the next infusion (10 April 2012), additional premedications included dimethindene and prednisolone. The infusion was completed as scheduled without dose interruptions or rate decreases, and the hypersensitivity event did not recur.

The investigator considered the event of hypersensitivity to be probably related to study treatment.

Subject No: MOR004-0020-4145 (13-year-old White female) Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/qow (MOR-004) Premedication(s): Cetirizine
Timing: During 7th infusion (2.25 hours after start of infusion) Adverse Event(s) and grade: Moderate hypersensitivity
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/qow) on 7 March 2012. On 18 April 2012, the subject received her 7th infusion with BMN 110 (2.0 mg/kg/qow), following premedication with cetirizine. Her pre-infusion vital signs taken at 8:55 AM included pulse 111 bpm, blood pressure 109/76 mmHg, temperature 37.1°C, and respiratory rate 24/minute. The infusion started at 9:15 AM at 6 ml/hr, and gradually increased to 72 ml/hr by 10:45 AM.

At 11:30 AM, the subject developed a non-serious moderate allergic reaction (symptoms not specified). Vital signs at that time included pulse 125, BP 113/75, temperature 36.5°C, and respiratory rate 24/minute. The infusion rate was decreased to 36 ml/hr, and after 15 minutes was interrupted. Treatment for the event included IV fluids, epinephrine, acetaminophen, prednisolone, dimethindene, and ranitidine.
At 2:20 PM, the infusion was restarted at 6 ml/hr, and increased to 12 ml/hr at 2:35 PM. Approximately 5 minutes later, the infusion was stopped and not completed on that date. The event of hypersensitivity was considered resolved by 3:40 PM. Vital signs during and after the infusion:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate
12:15 PM	134	124/86	38.5	24
1:15	140	100/70	38.1	24
2:10	135	104/70	38.1	
2:40	148	84/50	38	28
3:40	133	108/75	37.5	28
4:10	141	111/62	37.6	
5:10	123	108/74	37.5	

For the next infusion (25 April 2012), additional premedications included prednisolone and dimethindene. The infusion was completed as scheduled without dose interruptions or rate decreases, and the hypersensitivity event did not recur.

The investigator considered the event of hypersensitivity to be probably related to study treatment.

Subject No: MOR004-1073-4097 (12-year-old White male)

Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005) Premedication(s): Chlorphenamine
Timing: During 13th infusion in MOR-005 (20 minutes after start of infusion) Adverse Event(s) and grade: Grade 1 wheezing
Serious AE(s): No

This subject started treatment in MOR-004 (placebo) on 31 January 2012, and started treatment in MOR-005 (2.0 mg/kg/qow) on 19 July 2012. On 9 October 2012, he received his 13th infusion in MOR-005 (37th infusion overall), following premedication with chlorphenamine. His pre-infusion vital signs taken at 9:30 AM included pulse 84 bpm, blood pressure 136/69, temperature 35.6°C, and respiratory rate 32/minute. The infusion was

started at 6 ml/hr at 10:00 AM, and increased to 6 ml/hr at 10:15 AM.

At 10:20 AM, the subject developed non-serious grade 1 wheezing, as well as grade 1 peribuccal cyanosis, cough, and paleness. The infusion was stopped, and treatment for the events included IV hydrocortisone and inhaled salbutamol. Vital signs over the next hour:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate
10:20 AM	97	118/69	35.7	28
10:45 AM	102	95/68	36.2	36
11:00 AM	106	95/72	36.5	36
11:15 AM	90	95/60	36.5	32
11:32 AM	83	107/63	36.7	36

The events were considered resolved by 11:20 AM, and the infusion was restarted at 6 ml/hr. The infusion was gradually increased to 72 ml/hr by 12:50 PM, and it was completed without recurrence of the symptoms.

Premedications for the next infusion (17 October 2012) were changed to include hydrocortisone. The infusion was completed as scheduled, and the event of wheezing did not recur.

The investigator considered the event of wheezing to be probably related to study treatment.

Subject No: MOR007-0021-7009 (3-year-old Asian male) Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Acetaminophen, chlorphenamine, prednisolone
Timing: During the 24th infusion (3.25 hours after the start of the infusion) Adverse Event(s) and grade: Moderate hypersensitivity
Serious AE(s): No

This subject started treatment in MOR-007 (2.0 mg/kg/week) on 16 April 2012. In the 2-3 days prior to her 24th infusion, the subject complained of non-serious sneezing and sore throat. On 24 September 2012, the subject received his 24th infusion of BMN 110, following premedication with acetaminophen, chlorphenamine, and prednisolone. His pre-infusion vital signs taken at 10:10 AM included pulse 102 bpm, blood pressure 107/78, temperature 37.4°C, and respiratory rate 26/minute. The infusion was started at 3 ml/hr at 10:20 AM, and gradually increased to 36 ml/hr by 1:32 PM.

At 1:35 PM, the subject experienced a non-serious grade 2 hypersensitivity reaction. Treatment for the event included IV chlorphenamine and hydrocortisone. The infusion rate was decreased to 18 ml/hr at 2:02 PM, and then the infusion was discontinued completely at 2:08 PM. Vital signs during and after the infusion:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate	Oxygen saturation (%)
1:35 PM	108	114/64	37.8	46	100
2:20 PM	128	105/64	37.5	62	100
2:50 PM	142	112/83	37.5	40	98
3:48 PM	132	115/75	37.6	40	98

4:18 PM	142	119/86	37	44	97
5:18 PM	130	121/74	37.4	40	100
5:48 PM	115	93/68	36.9	36	99

The event of hypersensitivity was considered resolved as of 5:48 PM. This was the final infusion prior to the data cutoff for MOR-007 in the BLA, so it is not known whether the premedications for the next infusion were changed or whether the hypersensitivity event recurred with the next infusion.

The investigator considered the event of hypersensitivity to be probably related to study treatment.

Subject No: MOR007-0021-7013 (4-year-old White female)
Treatment Arm: BMN 110 2.0 mg/kg/week Premedication(s): Ranitidine, cetirizine, acetaminophen
Timing: 1 hour after the 18th infusion
Adverse Event(s) and grade: Grade 2 hypersensitivity
Serious AE(s): Yes

This subject started treatment in MOR-007 (2.0 mg/kg/week) on (b) (6). On (b) (6), the subject received her 14th infusion of BMN 110, following premedication of ranitidine, cetirizine, and acetaminophen. Her pre-infusion vital signs at 11:24 AM included pulse 100 bpm, blood pressure 118/85, temperature 37.6°C, and respiratory rate 25/minute. The infusion was started at 11:25 AM at 3 ml/hr, and increased to 6 ml/hr at 11:41 AM.

At 11:42 AM, the subject developed a sudden hypersensitivity reaction, with tachycardia, urticarial rash, and a feeling of agitation or distress. Vital signs at 11:45 AM included blood pressure 104/65, pulse 152, temperature 36.4°C, and oxygen saturation 97%. The infusion was stopped, and treatment for the event included IV chlorpheniramine and IV hydrocortisone. The patient's symptoms improved following this treatment, but because she remained tachycardic she was admitted overnight to the hospital for observation.
The infusion was not restarted. The event of hypersensitivity was considered resolved as of (b) (6)

Premedications for the next scheduled infusion (30 August 2012) included prednisolone, ranitidine, acetaminophen, and chlorphenamine. The infusion was completed as scheduled without dose interruptions or rate changes, and without recurrence of the hypersensitivity event.

The investigator assessed the event of hypersensitivity as probably related to study treatment.

Subject No: MOR007-1073-7011 (4-year-old White male) Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Chlorphenamine
Timing: Day of the 14th infusion (timing not specified) Adverse Event(s) and grade: Grade 1 wheezing
Serious AE(s): No

This subject started treatment in MOR-007 (2.0 mg/kg/week) on 14 May 2012.

On 10 August 2012, the subject received his 14th infusion with BMN 110, following premedication with chlorphenamine. The infusion was completed as scheduled without dose interruptions or rate changes. On the day of the infusion (timing not specified), the subject developed non-serious grade 1 wheezing and cough. Treatment for the events included inhaled beclomethasone and ambroxol. The events were considered resolved as of 14 August 2012.

The next scheduled infusion was given on 17 August 2012, and the infusion was completed as scheduled and without recurrence of wheezing.

The investigator considered the event of wheezing to be not related to study treatment.

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/s/

BANU A KARIMI SHAH
12/04/2013

LYDIA I GILBERT MCCLAIN
12/04/2013
I concur

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125460
Priority or Standard	Priority
Submit Date(s)	March 29 , 2013
Received Date(s)	March 29, 2013
PDUFA Goal Date	November 29, 2013 (Extension February 28, 2014)
Division / Office	Division of Gastroenterology and Inborn Errors Products
Reviewer Name(s)	Tamara Johnson, MD, MS
Clinical Team Leader	Jessica Lee, MD
Review Completion Date	November 25, 2013
Established Name	Elosulfase alfa
(Proposed) Trade Name	Vimizim
Therapeutic Class	Enzyme replacement
Applicant	Biomarin Pharmaceutical Inc.
Formulation(s)	Intravenous injection
Dosing Regimen	2.0 mg/kg/week
Indication(s)	Treatment of Mucopolysaccharidosis IVA (Morquio A syndrome)
Intended Population(s)	MPS IVA Patients aged 5 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This medical officer review evaluates BLA 125460 original application for Vimizim (elosulfase alfa). Elosulfase alfa 2 mg/kg once per week is proposed for use as an enzyme replacement therapy for the treatment of patients with Mucopolysaccharidosis Type IV A (MPS IVA, Morquio Syndrome) aged 5 years and older. The application was submitted by BioMarin Pharmaceutical Inc. (BioMarin) on March 29, 2013, and has been reviewed as part of the Program under the Prescription Drug User Fee Act (PDUFA) V. The application included a single Phase 3 adequate and well-controlled trial. BioMarin also included supportive trials: an ongoing Phase 3 extension trial, a completed Phase 1/2 trial and its extension trial, and two ongoing Phase 2 clinical trials.

This reviewer recommends approval of BLA 125460 with the requirement for postmarketing studies to demonstrate long-term clinical benefit and safety with use of the drug product. Additional perspective was sought from the Endocrine and Metabolic Drug Advisory Committee meeting on November 19, 2013 regarding the clinical meaningfulness of the results of the pivotal trial and additional long-term clinical outcomes to assess in the MPS IVA population. A boxed warning regarding risk of anaphylaxis is recommended for the full prescribing information.

The review of the clinical data is summarized here.

Efficacy
The Phase 3 trial (MOR004) compared two dosing regimens against placebo: elosulfase alfa 2 mg/kg weekly (QW) and elosulfase alfa 2 mg/kg every other week (QOW). The primary endpoint was the change in distance walked in the six-minute walk test (6MWT) from baseline to Week 24. Patients in the QW treatment group demonstrated a statistically significant mean change in the 6MWT of 22.5 meters (p-value = 0.02) when compared to placebo. Patients in the QOW treatment group performed similarly to those in the placebo group. The 23-meter difference between the QW and placebo groups is modest, but its clinical meaningfulness to the MPS IVA population is not clear. The results of the secondary endpoint, the change in three-minute stair climb (3MSC) rate from baseline to Week 24, did not demonstrate a statistically significant mean change (1.1 stairs/minute, p-value 0.49) when compared to placebo. The results of the secondary endpoint were similar across all three treatment groups. The results of the pharmacodynamic endpoint (change in normalized uKS from baseline to Week 24) demonstrated a sizeable response in both elosulfase alfa treatment groups after 4 weeks on treatment. Patients in the QW treatment group

experienced a mean reduction of 41% normalized uKS, while those in the QOW treatment group experienced a mean reduction of 30%.

In the open-label extension to Trial MOR004 (Trial MOR005), patients receiving elosulfase alfa QW or QOW rolled directly into Trial MOR005 without change in dosing regimen. Placebo patients were re-randomized to either the QW or QOW dosing regimen. Data from the first 48 weeks of this trial (72 weeks total time on treatment) have been reviewed. Patients who continued on the QW dosing regimen for another 48 demonstrated no improvement on the 6MWT over what was demonstrated in the 24 weeks of Trial MOR004. Some improvement was seen in the 3MSC endpoint; however, its importance could not be determined due to lack of a placebo comparison group.

Safety

The safety population comprised of all 235 patients enrolled in the six elosulfase alfa clinical trials submitted in the BLA application. The majority of patients (95%, 222 of 235) were treated with elosulfase alfa 2.0 mg/kg QW (the proposed marketing dosing regimen) for a duration from one week to 100 weeks.

- There were no deaths.
- Twenty-nine percent of patients had serious adverse events (SAEs), of which 10.6% were considered drug-related. Drug-related SAEs were commonly events of anaphylaxis, severe hypersensitivity, or reactions that occurred during infusion. Eighteen patients were determined to have had anaphylaxis, seven patients experienced serious hypersensitivity reactions and 20 patients had reactions during infusion which were SAEs. Two patients discontinued due to severe hypersensitivity reactions.
- The significant adverse events (AEs) for elosulfase alfa and all enzyme replacement therapies are anaphylaxis and hypersensitivity reactions. The incidence of anaphylaxis amongst MPS IVA patients treated with elosulfase alfa was 7.7%. This indicates 26 anaphylaxis events in 18 patients. Anaphylaxis occurred as early as 30 minutes from the time of infusion but as late as 3.25 hours after infusion. Anaphylaxis occurred as late into treatment as the 47th infusion.
- Hypersensitivity reactions were reported in 64 (27%) patients. Recurrent hypersensitivity reactions were frequently demonstrated in those who experienced hypersensitivity. The most commonly reported hypersensitivity reactions were angioedema (25%), urticaria (9%), “hypersensitivity” (5%), peripheral edema (5%), wheezing (4%), flushing (2%), cough (2%) and nasal obstruction (2%).
- The most common adverse reactions occurring in ≥10% of patients treated with elosulfase alfa (safety population, n=235) included pyrexia (26%), vomiting (22%), headache (20%), nausea (18%), abdominal pain (14%), and fatigue (12%). In MOR-004, the most common adverse reactions occurring in ≥10% of patients treated with elosulfase alfa and with a higher incidence than in the placebo-treated patients were pyrexia (33%), vomiting (31%), headache (26%), nausea (24%), abdominal pain (21%), chills (10%) and fatigue (10%).

Immunogenicity
All patients treated with elosulfase alfa developed high titers of anti-drug antibodies (including neutralizing antibodies) that remained elevated over the 72-week treatment period. The impact of anti-drug antibodies on safety and efficacy is unknown, but it is possible that these antibodies interfered with the successful uptake of the drug into the cell lysosome.

1.2 Risk Benefit Assessment

Elosulfase alfa 2 mg/kg once per week is proposed for treatment of a rare, inherited, metabolic disease, MPS IVA. This disease is characterized by progressive skeletal dysplasia, short stature, and poor respiratory function. The majority of patients has the severe disease phenotype and usually dies in the second or third decade of life. If approved, elosulfase alfa would be the only therapy available for this serious life-threatening disease. There is no current FDA-approved medication available to treat MPS IVA patients.

The pivotal trial (MOR004) demonstrates a statistically significant improvement in the primary efficacy measure, the change in 6MWT distance. The degree of improvement on the 6MWT was not reflected in the secondary or tertiary efficacy measures; therefore, the clinical meaningfulness of the change on 6MWT is not clear. In the open-label extension trial (MOR005), there was no worsening of the 6MWT performance from week 24 and the secondary endpoint demonstrated more improvement by week 72. Because the changes demonstrated in Trial MOR005 must be interpreted with caution due to lack of a comparator arm, long term durability of treatment benefit must be evaluated in future trials. Additional clinical outcome measures, which are more disease-specific and measurable over a longer time period, may aid in resolving both issues of meaningfulness of the 6MWT results and durability of effect.

There are known safety risks with elosulfase alfa treatment. The risk of anaphylaxis is moderate (~8%) and recurrent hypersensitivity reactions were frequently demonstrated in those who experienced hypersensitivity. There is a high probably of developing and maintaining high titers of anti-drug antibodies, including those that neutralize cellular uptake of elosulfase alfa. The impact of high anti-drug antibody titers on the efficacy results is unknown at this time and will require additional study to determine. Although there may be potential for improved clinical benefit with implementation of an immune tolerance induction program, this approach has risks of immune suppression, including frequent respiratory infections in a population already known for respiratory conditions. Table 1 summarizes the benefits and risks associated with elosulfase treatment.

Table 1: Summary of Benefits and Risks with Elosulfase Alfa Treatment

Benefits	Risks
• Elosulfase alfa would be the only therapy available for this serious life-threatening disease • Efficacy was demonstrated over the initial 24 weeks of treatment, with no worsening for an additional 48 weeks of treatment • There is potential for improved benefit with immune tolerance induction	• High probably of developing anti-drug antibodies, including those that neutralize uptake of elosulfase alfa into cells, which may impact efficacy or safety • Risk of anaphylaxis and recurrent hypersensitivity reactions • Long term durability of treatment benefit is unknown

Despite the risks associated with elosulfase alfa, patients will seek elosulfase alfa treatment because it would be the only available therapy for MPS IVA disease. Therefore, MPS IVA patients who receive elosulfase alfa treatment should be assured that the therapy provides substantial and durable clinical benefit. Additional study is needed to evaluate the clinical benefit of elosulfase alfa beyond 72 weeks of treatment. Long term clinical outcome measures should examine elosulfase alfa's effect on growth, progression of skeletal deformities, musculoskeletal function, as well as frequency of orthopedic surgery. Lastly, the potential for mitigating patient immunogenic response to elosulfase alfa over time (natural or induced) needs to be assessed, such that a clear conclusion about anti-drug antibody impact on efficacy and safety may be determined. Proposed postmarketing requirements listed below in Section 1.4 of this document will attempt to address these needs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no current recommendations for postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no obligations for the Pediatric Research Equity Act (PREA) because orphan products are exempt from requirements under PREA. Elosulfase alfa received orphan drug designation on May 15, 2009.

Listed below are recommendations for postmarketing requirement studies to further evaluate the efficacy and safety of elosulfase alfa in the MPS IVA population.

- (b) (4)
- (b) (4) Evaluate the (b) (4) of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with elosulfase alfa who are at high risk of developing persistent neutralizing antibody. This immune tolerance regimen will be implemented before or concomitant with onset of elosulfase alfa therapy. (b) (4)
- (b) (4)

Discussions regarding the goal dates and details of the study requirements are ongoing at the time of this review.

2 Introduction and Regulatory Background

2.1 Disease Background

Mucopolysaccharidosis IV Type A (MPS IVA) or Morquio syndrome Type A, is a rare, lysosomal storage disease caused by mutation in the gene for the lysosomal enzyme N–acetylgalactosamine 6-sulfatase (GALNS). Without functional GALNS enzyme, the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate are not degraded and accumulate within the cell lysosome. This accumulation leads to dysfunction in bodily tissues and organs.

MPS IVA is associated with more than 180 mutations of the GALNS gene.[1] The mutations span the entire gene and have been identified in over 400 mutant alleles. The frequency of GALNS gene mutations in the MPS IVA population have been reported as missense mutations (69-78%), splice site mutations (9%), small deletions (9-12%), nonsense mutations (5-6%), large deletions (1-2%) and insertions (2-3%).[1,2] The ten most frequent mutations represent 35% of all described mutations and are single nucleotide changes, except for one deletion.[3] The following three missense mutations account for over 5% of all mutations: R386C, G301C, and I113F.

MPS IVA is inherited in an autosomal recessive manner and affects both genders and all ethnicities. The estimated incidence in the US is 1:200,000 to 1:300,000 live births, with approximately 520-800 prevalent cases. Patients come to the attention of a physician due to skeletal abnormalities and increased levels of keratan sulfate in urine. The diagnosis is confirmed by deficient enzyme levels in white blood cells or fibroblasts, or confirmed by genetic analysis.

Disease presentation and progression vary by patient. Patients with more progressive (severe) disease phenotype typically present with bone dysplasia at birth and die in the 2nd or 3rd decade of life. Patients with attenuated (mild) disease phenotype may be diagnosed as late as adulthood. They have less bone deformity and have been reported to live into their sixties. Although a severe phenotype has not been formally established, some clinicians have based their determination of severity on the patient's height. This approach is supported by the observation that patients categorized with severe phenotype have a reduced growth rate beginning at age 18 months and stop growing at approximately 7 or 8 years-old.[3] Final height is typically eight standard deviations less than the mean height for healthy controls. Patients categorized with mild phenotype, however, continue to grow during adolescence. Montano *et. al* used final height for the categorization of severity in the International Morquio A Registry.[4] The majority of patients were reported to have severe phenotype: 68% with severe phenotype (height <120 cm), 10% with mild phenotype (height >140 cm), and another 15% with an intermediate type (120-140 cm). This is consistent with a review of MPS IVA mutations by Dung VC *et al.* where 69% of mutations were associated with severe phenotype, 19% with attenuated, and another 12% were undefined.[5] MPS IVA patients

1 Hendriksz CJ, Harmatz P, Beck M, Jones S, Wood T, Lachman R, Gravance CG, Orii T, Tomatsu S. Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA. Mol Gen Metab 110(2013): 54-64.
2 Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 253000: 10 January 2011: . World Wide Web URL: http://omim.org/
3 Hendriksz CJ, Harmatz P, Beck M, Jones S, Wood T, Lachman R, Gravance CG, Orii T, Tomatsu S. Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA. Mol Gen Metab 110(2013): 54-64.
4 Montano A.M., Tomatsu S., Gottesman G.S., Smith M., Orii T., International Morquio A Registry: clinical manifestation and natural course of Morquio A disease, J. Inherit. Metab. Dis. 30 (2) (2007) 165–174.
5 Dung VC, Tomatsu S, Montano AM, Gottesman G, Bober MB, Mackenzi W, Maeda M, Mitchell GA, Suzuki, Y, Orii T. Mucopolysaccharidosis IVA: Correlation between genotype, phenotype and keratan

with mutations associated with a severe phenotype have been demonstrated to have no GALNS enzyme activity.[6] Those with mild phenotype have 1-13% residual enzyme activity.

The clinical features of MPS IVA include progressive skeletal dysplasia (including joint deformities/contractures, short stature, spinal cord compression), restrictive lung disease, valvular heart disease, hearing loss, cataracts, and corneal clouding. Unlike other mucopolysaccharidoses, MPS IVA patients have normal intelligence. It is, however, the musculoskeletal and respiratory dysfunctions that have the greatest impact on these patients' lives. Patients describe most bothersome symptoms as fatigue, decreased endurance, joint stiffness and pain.[7] Up to one-third of MPS IVA patients who walk require a walking aid to ambulate.[8] Patients with severe disease are usually wheelchair-bound by adolescence. Chest deformities, such as pectus carinatum, lead to restrictive lung disease, while laryngeal narrowing and tracheobronchial abnormalities may cause obstructive lung disease. Death is due to respiratory failure, cardiac disease, or CNS complications (i.e., atlantoaxial subluxation, spinal cord compression).[9]

There are no FDA-approved treatments for MPS IVA disease. Patients receive supportive therapy to address symptoms (i.e., pain medication, antibiotics, oxygen). Many patients undergo surgical procedures to improve skeletal conditions with varying degrees of success. In the International Morquio A Registry, 56% of patients had one or more surgeries. The most frequent surgeries were cervical spinal cord decompression/fusion 51%), ear tube placement (33%), osteotomy (26%), and hip reconstruction and replacement (25%).[9] Bone marrow transplantation has not been shown to improve clinical outcome.[10]

2.2 Product Information

Vimizim (elosulfase alfa, BMN 110) is a recombinant human enzyme N–acetylgalactosamine 6-sulfatase produced in Chinese hamster ovary cell line. Vimizim is a soluble dimeric protein, and each monomer contains 496 amino acids with an approximate molecular mass of 55 kDa. The oligosaccharides present at the two consensus N-linked glycosylation sites contain mannose-6-phosphate (M6P). M6P residues allow specific binding of the enzyme to the M6P receptors on the cell surface,

sulfate levels. Mol Gen Metab 110 (2013): 129-138.
6 Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 253000: 10 January 2011: World Wide Web URL: http://omim.org/
7 MPS IVA Patient Teleconference with FDA regarding most troublesome symptoms.
8 Harmatz P *et al.* Mol.Genet Metab 2013.
9 Montano A.M., Tomatsu S., Gottesman G.S., Smith M., Orii T., International Morquio A Registry: clinical manifestation and natural course of Morquio A disease, J. Inherit. Metab. Dis. 30 (2) (2007) 165–174.
10 Bouzidi H, Khedhiri S, Laradi S, Ferchichi S, Daudon M, Miled A. [Mucopolysaccharidosis IVA (Morquio A syndrome): clinical, biological and therapeutic aspects]. Ann Biol Clin (Paris). 2007 Jan-Feb;65(1):5-11.

leading to cellular internalization of the enzyme, and targeting of intracellular lysosomes. Inside the lysosome, the enzyme cleaves the sulfate groups from the keratan sulfate and chondroitin-6-sulfate molecules, preventing their accumulation in cells and disruption of organ function.

Vimizim is a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution that must be diluted with 0.9% normal saline solution to be administered by intravenous infusion.

2.3 Tables of Currently Available Treatments for Proposed Indications

None

2.4 Availability of Proposed Active Ingredient in the United States

The active ingredient of Vimizim is not available in the United States, or outside the United States.

2.5 Important Safety Issues With Consideration to Related Drugs

Vimizim is the first enzyme replacement therapy (ERT) intended to treat MPS IVA; however, other ERTs are available for other mucopolysaccharidoses. Approved ERTs for lysosomal storage diseases are listed below in Table 2.

Table 2: Reviewer's Table -- FDA-Approved Enzyme Replacement Therapies for Lysosomal Storage Diseases

ERT	Disease	Approval Year
Cerezyme	Gaucher Disease	1991
Fabrazyme	Fabry Disease	1993
Aldurazyme*	MPS I – Hurler's Syndrome	2003
Naglazyme	MPS VI – Maroteaux-Lamy Syndrome	2005
Elaprase*	MPS II – Hunter's Syndrome	2006
Myozyme*	Pompe Disease	2006
Lumizyme*	Late-Onset Pompe Disease	2010
VPRIV	Gaucher Disease	2010

* The full prescribing information for these drug products have a boxed warning for anaphylaxis.

The main safety issue with all ERTs is the development of anti-drug antibodies and the expected hypersensitivity reactions including risk of anaphylaxis. The majority (50-90%) of patients treated with ERTs develop antibodies specific against the recombinant

enzyme and severe hypersensitivity reactions are to be expected during drug infusion.[11] These reactions are often IgG-mediated; however, IgE-mediated reactions and anaphylaxis have occurred in patients. These hypersensitivity reactions are usually managed by premedicating patients with antihistamines, antipyretics and corticosteroids; slowing or stopping infusion; and (with anaphylaxis) emergent medical care. Due to the risk of anaphylaxis, a boxed warning is being incorporated into the full prescribing information for ERT drug products for inborn errors of metabolism disorders.

Medical Officer's Comment
Immune tolerance induction programs are being investigated to improve efficacy and safety in patients with strong immunologic response to ERT drug products. They have been successful in patients with Pompe disease, Gaucher disease, and hemophilia A.[12] In an immune tolerance induction program, patients are co-administered the ERT with an immunosuppressive drug, with the goal to reduce the antibody response to the drug antigen. Despite the risks of infection and malignancy associated with immunosuppressive therapy, tolerance induction programs may be worthwhile for the rare disease community who often only has one option for drug therapy.

2.6 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant, BioMarin Pharmaceuticals, Inc., has had a long history of interaction with the Division:

- **March 2008 - Type C meeting**: To discuss the proposed nonclinical plan in support of the Phase 1/2 study. The Division did not agree with the nonclinical plan and recommended a long-term study of the repeat-dose toxicology study in cynomolgus monkeys (9 months duration) and a repeat dose toxicology study in rats (6 months duration) prior to the first-in-human study.

- **July 2010 -Type B Pre IND/End-of-Phase 2 meeting:** To present the results of the Phase 1/2 study and discuss the proposed Phase 3 clinical study design and the adequacy of the CMC, nonclinical and clinical programs to support a BLA submission. As of this meeting, all data had been collected outside the US. The Division expressed concern about the proposed Phase 3 study dose of 2 mg/kg/week, as this dose was not adequately justified based on the results of the Phase 1/2 Trial (MOR-002). The Division indicated that because the dose escalation scheme in MOR002 was sequential within patients, it is difficult to

11 Burrow TA, Hopkin RJ, Leslie ND, Tinkle BT, Grabowski GA. Enzyme reconstitution/replacement therapy for lysosomal storage diseases. Curr Opin Pediatr. 2007 Dec;19(6):628-35.
12 Wang J, Lozier J, Johnson G, Kirshner S, Verthelyi D, Pariser A, Shores E, Rosenberg A. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention and treatment. Nat Biotechnol 2008; 26 (8):901-8.

determine whether therapeutic benefit is due to dose level or treatment duration. The Division recommended that BioMarin conduct a separate Phase 2 dose-finding study. The Division expressed concern regarding limited dose-safety response relationship and advised the BioMarin to submit a Special Protocol Assessment (SPA).

- **December 2010 - Special Protocol Assessment**: To obtain further feedback on the Phase 3 pivotal study design. The Division agreed that 6MWT could be used as a primary endpoint; however, the (b) (4) The Division advised BioMarin to revise their primary analysis plan to include an (b) (4) or, otherwise, define a clinically meaningful definition of response and analyze the primary endpoint using a responder analysis. The Applicant was asked to define and provide support for a clinically relevant minimal clinically important difference (MCID) for the MPS IVA patient population. The Division stated that differences in 6MWT observed in clinical trials of other lysosomal storage disorders were not sufficient to justify a MCID in the MPS IVA population. BioMarin agreed to revise the Safety Management Plan for the Phase 3 study per the Division's recommendations. BioMarin agreed to evaluate the effect of elosulfase alfa in patients less than 5 years of age. A No Agreement letter was issued on January 20, 2011.

- **July 2012 - Type C meeting [written feedback only]**: To reach agreement on clinical and statistical aspects of the clinical development plan. The Division stated concerns that the Phase 3 trial may not provide substantial evidence of benefit and that BioMarin should consider previously provided recommendations regarding study dose, dosing regimen and study endpoints. BioMarin determined that further discussion was not required and cancelled the meeting.

- **November 2012 - Type C meeting:** To obtain feedback on CMC topics related to the BLA submission. There was general agreement with the proposed CMC package for submission; however, the Division advised on additional required components to be included in the submission. For instance, BioMarin was advised to include validation data summaries supporting the aseptic process and sterility assurance and was referred to the "Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994)." The Division agreed to accept 6-month stability data for the drug product within 30 days of the BLA submission.

- **December 2012 - Type B pre-BLA meeting:** To discuss clinical and nonclinical aspects of the elosulfase alfa clinical program and to reach agreement on the content and format of the proposed BLA submission. The Division agreed that the proposed nonclinical package appeared adequate to support the BLA, provided that a carcinogenicity assessment is included. BioMarin agreed to the Division's

request to provide 1 year of safety and efficacy data from at least 50 patients exposed to the proposed marketing dose (i.e., 2 mg/kg/week). The Division agreed to BioMarin's proposal to provide abbreviated clinical study reports for the ongoing studies and BioMarin agreed to provide the Division with datasets from the ongoing studies. The Division also expressed concern about the demonstration of efficacy in the Phase 3 trial and highly recommended that a longer (1-2 duration) placebo-controlled trial to evaluate the efficacy of elosulfase alfa in MPS IV patients be conducted. Such a controlled trial could definitively determine if continued improvement in efficacy measures are attributable to a treatment effect. Without a controlled trial, there is uncertainty whether the trends toward improvement in the efficacy measures seen in the Phase 3 extension study are related to an elosulfase alfa treatment effect.

BioMarin is seeking marketing authorization in Europe concurrently with this BLA review. The pre-submission meetings with EMA were held in November 2012.

Medical Officer's Comment
BioMarin has complied with all of the Division's recommendations from the pre-BLA meeting; except for the recommendation to conduct a longer (1-2 year duration) randomized controlled trial to support durability of efficacy results. Currently, the clinical meaningfulness of the modest improvement in the 6MWT during the 24-week Phase 3 trial is not clear.

2.7 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was good. It was well-organized with appropriate links in place to allow easy navigation to supporting documents. Bookmarks were adequate in the clinical study reports. BioMarin was responsive to the multiple information requests issued by the review team.

3.2 Compliance with Good Clinical Practices

Trial MOR004 was conducted in accordance with the following:

- United States (US) Code of Federal Regulations (CFR) sections that address clinical research studies; Eudralex Volume 10 – Clinical Trial guidelines; and/or other national and local regulations, as applicable
- ICH E6
- The ethical principles established by the Declaration of Helsinki

The study was based on adequately performed laboratory and animal experimentation, conducted under a protocol reviewed and approved by the Institutional Review Board (IRB), Independent Ethics Committee (IEC) or Research Ethics Board (REB), conducted by scientifically and medically qualified persons. The benefits of the study were in proportion to the risks and the rights and welfare of patients were respected. The physicians conducting the study did not consider the hazards to outweigh the potential benefits of patient participation.

A properly written and executed informed consent form (ICF), in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), US 21 CFR §50, and applicable local regulations, was obtained for each patient prior to enrollment in the study. A patient younger than 18 years of age (or defined as a minor, depending on the region) provided written assent (if required) and his/her legally authorized representative (parent or legal guardian) provided written informed consent for such patients.

An independent Data Monitoring Committee (DMC) was responsible for monitoring the safety and safeguarding the interests of study participants, assessing the safety and efficacy of study interventions, and monitoring overall study conduct. The DMC chairperson reviewed the cumulative data available for the first 12 patients enrolled in the study who had received at least 4 weeks of study drug infusions (i.e., the gating cohort) to recommend whether to allow global enrollment to continue. The DMC met approximately every 4 months, with additional meetings if necessary, to review analysis reports provided by an Independent Statistical Center. DMC recommendations may have impacted patient management and retention, improving adherence to protocol-specified regimens, data management, and quality control.

An independent Allergic Reaction Review Board (ARRB), comprised of at least one allergist/immunologist and physicians not directly involved with the study, was available for consultation during the review of severe hypersensitivity or reactions associated with infusion.

3.3 Financial Disclosures

BioMarin submitted an FDA form 3454 for each clinical study certifying that it had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could have affected the outcome of the study. In addition, no investigator has reported proprietary interest in Vimizim or held a significant equity in BioMarin. However, several principal investigators (listed below) have received financial compensation from BioMarin for serving on the steering committee for (b) (4) and other trials under the Vimizim clinical development program.

Clinical Investigators:

(b) (6)

Other Important Study Participant:

(b) (6)

A Steering Committee (SC) of MPS IVA clinical experts included selected investigators from Trial MOR (b) (4), at least one BioMarin representative, and one external biostatistician. The SC provided guidance to BioMarin and MOR (b) (4) investigators relating to study design and execution, interpretation of unblinded results, and dissemination of findings.

Due to their (b) (4), financial endorsements and significant involvement of (b) (6) n multiple BioMarin protocols, their clinical sites were selected for inspection.

Table 3: Results of Trial MOR004 Selected Clinical Sites Inspection

Site Number	Prinicipal Investigator	Study Site Location	Number of Patients Enrolled	Inspection Classification
(b) (6)				VAI: Deviation(s) from regulations.
				NAI: No deviation from regulations.
(b) (6)				VAI: Deviation(s) from regulations.

Two clinical study sites had VAI issues considered deviation from the regulations, but the issues do not appear to impact the contribution of the respective clinical study site to the overall efficacy and safety results of Trial MOR (b) (4)

- At site (b) (4), it was noted that the thermometer had not be calibrated in the area where the study drug was stored. Although daily temperature minimums and maximums were recorded, no records were available for any maintenance, monitoring, or testing since installation of the thermometer. There is concern that the stability of the product may be impacted if there were improper storage temperatures.
- At site #1073, vital signs taken within 30 minutes of termination of infusion were recorded as taken during infusion. This appeared to be a deviation from the investigational plan; however, the misplaced recording of this last vital sign was consistent in the case report forms. There were also two instances were redness of the tympanic membrane were not reported as adverse events. These issues represent inadequate record keeping at site #1073, rather than protocol violation and do not significantly impact the data integrity.

The conclusion of the three clinical site inspections determined that the trial appears to have been conducted adequately, and the data generated by these sites may be used in support of the indication. Additional details regarding these inspections are provided in the Clinical Inspection Summary by Dr. S. Leibenhaut, dated October 24, 2013.

Medical Officer Comment
The VAI issue of site (b) (4) thermometer uncalibrated) was considered in light of potential impact on efficacy and safety. Study site patient results on the primary endpoint were consistent with the rest of the study population, and had no outliers. There were also no outstanding findings in regards to the incidence of serious adverse reactions or immunologic response from study site patients. It appears that, despite an uncalibrated thermometer, the study site experience was not compromised.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The review of data submitted to support the well-controlled manufacturing of a pure and potent elosulfase alfa are adequate; however, there is continuing concern about stability of the drug product being prepared for marketing. The drug product manufactured at two different sites demonstrates significant differences in degradation rates. This

makes the drug product for marketing less stable compared to that used in clinical trials. In addition, only data for a 12-month period has been submitted and will not support a (b) (4) expiry date. Therefore, additional studies have been requested and are pending receipt from BioMarin. For additional details, refer to the Chemistry Manufacturing and Controls review by C. Ausin and R. Ledwidge for this original BLA submission.

4.2 Clinical Microbiology

Elosulfase alfa is a sterile, preservative-free 1 mg/ml solution for infusion. The drug product is manufactured by (b) (4) single-use vials. The application included sufficient data supporting microbial control of the drug substance manufacturing process and sterility assurance of the drug product. Although the late submission of bacterial endotoxin and rabbit pyrogen tests delayed the review, the result of the tests is not expected to have a negative impact on patient safety. There are no microbiology issues that would preclude approval; however, postmarketing commitments are being considered to address accurate assessment of endotoxin release from the drug substance and drug product at the time of this review. For additional details, refer to the Clinical Microbiology review by Dr. C. Thomas and C. Gomez-Broughton for this original BLA submission.

4.3 Preclinical Pharmacology/Toxicology

BioMarin conducted safety pharmacology studies in rats and monkeys, pharmacokinetic/toxicokinetic studies in rats, mice, and monkeys, and repeat-dose toxicology studies of up to 26 weeks in rats and 52 weeks in monkeys. In repeat-dose toxicology studies, anti-drug antibody (including neutralizing antibody) development in most animals may have contributed to prolonged t ½ and higher systemic exposure. Anaphylactic reaction was demonstrated in rats, although all rats received diphenhydramine premedication. No target organ toxicity was seen in either species up to 20 mg/kg repeated dose. The Pharmacology/Toxicology reviewer believes that neutralizing antibodies may have eliminated potential toxicologic targets and is cautious about conclusions from these studies.

Reproductive and developmental toxicity was evaluated in rats and rabbits. Elosulfase alfa had no effect on fertility and embryo-fetal development parameters; however, toxicity was noted in the prenatal/postnatal study. With the rats, three deaths during pregnancy occurred due to anaphylaxis or diphenhydramine toxicity, but these deaths demonstrated no dose-response relationship. On the other hand, the higher dose groups (6 and 20 mg/kg/day elosulfase alfa) had more stillbirths than the lower dose group (1 mg/kg/day elosulfase alfa). Rat pup death in the 20 mg/kg/day group was 3%

higher that the diphenhydramine alone group during the two to four days postpartum, raising concern about *in utero* exposure.

For additional details, refer to the Pharmacology/Toxicology review by Dr. F. Cai for this original BLA submission.

Medical Officer Comments
Elosulfase alfa is excreted in milk, as the sponsor has reported in the labeling; however, (b) (4) ***are not reflected in the labeling. Because the drug crosses the placenta into the fetal circulation, as evidenced by the reproductive rabbit study, the rat pup deaths are likely due to delayed reaction from in utero exposure. The Pharmacology/Toxicology reviewer is recommending a Pregnancy Category of C and had made further labeling changes in Sections 8, 12, and 13 of the full prescribing information. This reviewer agrees with the labeling changes.***

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Elosulfase alfa is a recombinant human enzyme N-acetylgalactosamine-6-sulfatase that provides the action of cleaving sulfate esters from the glycosaminoglycans keratan sulfate and chondroitin 6-sulfate. This enzyme activity allows transport of the glycosaminoglycans out of the cell lysosomes, thereby reducing tissue and organ dysfunction associated with their accumulation.

4.4.2 Pharmacodynamics

The pharmacodynamic effect of elosulfase alfa was demonstrated in changes of normalized urine keratan sulfate from baseline (uKS). In Trial MOR004, the normalized uKS levels decreased from baseline to Week 24 in both elosulfase alfa 2 mg/kg QOW and elosulfase alfa 2 mg/kg QW treatment groups by 30% and 41%, respectively. Further discussion of changes in uKS are provided in Section 6.1.5 Analysis of Secondary Endpoints(s) of this document.

4.4.3 Pharmacokinetics

The pharmacokinetic profile (PK) of elosulfase alfa was determined in 24 and 23 MPS IVA patients who received 2 mg/kg dose every other week and once per week in trial MOR-004, respectively. PK samples were taken at Weeks 0 and 22 at selected sites pre-dose within 15 minutes before infusion, 60 and 120 minutes after infusion start,

within 5 minutes before stopping infusion, and 5, 15, 30, 60, 120, and 180 minutes post-infusion. By Week 22, mean t 1/2, mean AUC and Cmax increased two- to five-fold the measurements at Week 0. These increases are believed to have been influenced by patient anti-drug antibody status (binding and neutralizing antibodies). See Section 7.4.6 Immunogenicity, for details regarding anti-drug antibody development in MPS IVA patients treated with elosulfase alfa.

Contrary to increases demonstrated in the other PK parameters, mean clearance decreased by 30% at Week 22. Clearance of elosulfase alfa was inversely correlated with age (higher in patients ≤ 17 years, n=22) and body weight (higher in patients with lower body weight, n=7). The clearance of elosulfase alfa 2 mg/kg/week by race demonstrates a slower clearance in Asian patients (n=12) when compared to White patients (n=31) both at Week 0 and Week 22. Because the number of adult and Asian patients who were evaluated for the PK study is small, the clinical relevance of the observed differences in elosulfase alfa clearance is not clear. PK parameters at Week 0 and Week 22 are shown below in Table 4: Pharmacokinetic Profile of Elosulfase Alfa. For additional details, refer to the Clinical Pharmacology review by Dr. C. Hon for this original BLA submission.

Table 4: Pharmacokinetic Profile of Elosulfase Alfa

Pharmacokinetic Parameter	Week 0 (N = 22) Mean (SD)	Week 22 (N=22) Mean (SD)
AUC_{0-t}, min x µg/mL[*]	238 (100)	577 (416)
C_{max}, µg/mL[†]	1.49 (0.534)	4.04 (3.24)
T_{max}, min[Þ]	172 (75.3)	202 (90.8)
CL, mL/min/kg[‡]	10.0 (3.73)[a]	7.08 (13.0)[c]
V_{dss}, mL/kg[§]	396 (316)[b]	650 (1842)[c]
$t_{1/2}$, min[#]	7.52 (5.48)[a]	35.9 (21.5)[c]

[*] AUC_{0-t}, area under the plasma concentration-time curve from time zero to the time of last measurable concentration;
[†] C_{max}, observed maximum plasma concentration;
[Þ] $T_{max,}$ time from zero to maximum plasma concentration;
[‡] CL, total clearance of drug after intravenous administration;
[§] V_{dss}, apparent volume of distribution at steady-state;
[#] $t_{1/2}$, elimination half-life;
[a] N = 15;
[b] N = 14;
[c] N = 20

From BioMarin's Table 2.7.2.2.1.1, Module 2.7.2 Summary of Clinical Pharmacology Studies.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Six clinical trials, including 2 completed trials and 4 ongoing trials, are presented in this application. The completed randomized, double-blind, placebo-controlled Phase 3 Trial MOR-004 is the pivotal trial supporting this new biologics license application, along with supportive data from the Phase 1/2 Trial MOR-002, two ongoing long-term extension trials (MOR-005 and MOR-100), and two ongoing ancillary Phase 2 trials (MOR-007 and MOR-008). A seventh ongoing Phase 2 trial (MOR-006) is not presented in this marketing application due to incomplete enrollment and very limited exposure at the time of data cutoff. Table 2 summarizes each clinical trial.

Table 5: Clinical Trials of Elaprase

Type of Trial	Trial Identifier	Objective(s)	Trial Design and Type of Control	Dosing Regimen and Route of Administration	Number of Patients	Patient Population	Duration	Trial Status; Type of Report Submitted
Efficacy, Safety, PK	MOR-004	Primary objective: • To evaluate the ability of 2.0 mg/kg/week elosulfase alfa and 2.0 mg/kg/every other week elosulfase alfa compared with placebo to enhance endurance in patients with MPS IVA, as measured by an increase in the number of meters walked in the 6 minute walk test (6MWT) from Baseline to Week 24.	Phase 3, Multinational, Multicenter, Double-blind, Placebo-controlled Trial	elosulfase alfa 2.0 mg/kg/week *or* 2.0 mg/kg/every other week *or* Placebo 4 hour intravenous (IV) infusions	177 randomized 176 dosed	MPS IVA patients age 5 years and older who are able to walk ≥ 30 and ≤ 325 meters in the 6MWT	24 weeks	Complete; Full CSR
Safety, Efficacy	MOR-005	Primary objective: • To evaluate the long-term safety and efficacy of elosulfase alfa administration at 2.0 mg/kg/week or 2.0 mg/kg/every other week in patients with MPS IVA.	Phase 3 Extension, Multinational, Multicenter, Double-Blind followed by Open-Label Trial	Double-blind phase: elosulfase alfa 2.0 mg/kg/week *or* 2.0 mg/kg/every other week Open-label phase: elosulfase alfa 2.0 mg/kg/week (dose determination based on the final primary efficacy and safety analyses from MOR-004) 4 hour intravenous (IV) infusions	173	MPS IVA patients who completed MOR-004	Up to Week 240	Ongoing; CSR containing complete safety data and all available efficacy data from all patients collected up to the data cut-off date of 04JAN2013

Type of Trial	Trial Identifier	Objective(s)	Trial Design and Type of Control	Dosing Regimen and Route of Administration	Number of Patients	Patient Population	Duration	Trial Status; Type of Report Submitted
Safety, PK, Efficacy	MOR-002	Primary objective: • To evaluate the safety of weekly infusions of elosulfase alfa administered in escalating doses to patients with MPS IVA.	Phase 1/2, Multicenter, Open-Label, Dose-Escalation Trial	Dose-Escalation Period: elosulfase alfa • Weeks 1-12: 0.1 mg/kg/week • Weeks 13-24: 1.0 mg/kg/week • Weeks 25-36: 2.0 mg/kg/week Optional continuation period: elosulfase alfa 1.0 mg/kg/week for an additional 36-48 weeks. 4 to 5 hour intravenous (IV) infusions	20	MPS IVA patients age 5-18 years	Dose escalation period: 36 weeks Optional continuation period: 36-48 weeks Total trial duration: 72-84 weeks	Complete; Full CSR
Safety, Efficacy	MOR-100	Primary objective: • To evaluate the long-term safety and efficacy of weekly infusions of 2.0 mg/kg of elosulfase alfa administered in patients with MPS IVA who participated in MOR-002	Multicenter, Open-Label, Extension Trial	elosulfase alfa 2.0 mg/kg/week 4 hour intravenous (IV) infusions	17	MPS IVA patients who completed MOR-002	Up to 240 weeks	Ongoing; CSR containing complete safety data and all available efficacy data from all 17 patients collected up to the data cut-off date of 19JUL2012

Type of Trial	Trial Identifier	Objective(s)	Trial Design and Type of Control	Dosing Regimen and Route of Administration	Number of Patients	Patient Population	Duration	Trial Status; Type of Report Submitted
Safety, Efficacy	MOR-006	Primary objective: • To evaluate the efficacy and safety of weekly intravenous (IV) infusions of 2.0 mg/kg elosulfase alfa in MPS IVA patients with limited ambulation (efficacy as defined by the domains of upper extremity function and dexterity, mobility, pain and self-care functional abilities).	Phase 2, Multinational, Open-Label Trial	elosulfase alfa 2.0 mg/kg/week 4 hour intravenous (IV) infusions	Approx. 20 (planned) 2 enrolled as of 14 Sep 2012	MPS IVA patients age 5 years and older who have limited ambulation, defined as an inability to walk ≥ 30 meters in the 6MWT	48 weeks	Ongoing; No report will be included in the marketing application due to limited data available as of the data cut-off date of 14SEP2012

Type of Trial	Trial Identifier	Objective(s)	Trial Design and Type of Control	Dosing Regimen and Route of Administration	Number of Patients	Patient Population	Duration	Trial Status; Type of Report Submitted
Safety, Efficacy	MOR-007	Primary objective of the primary treatment phase: • To evaluate safety and tolerability of infusions of elosulfase alfa at a dose of 2.0 mg/kg/week over a 52-week period in MPS IVA patients less than 5 years of age Primary objective of the extension phase: • To evaluate the long-term safety of elosulfase alfa at a dose of 2.0 mg/kg/week in patients with MPS IVA less than 5 years of age at enrollment	Phase 2, Multinational, Open-Label Trial	elosulfase alfa 2.0 mg/kg/week 4 hour intravenous (IV) infusions	15 with 8 patients <5 (but ≥3) years of age (actual)	MPS IVA patients less than 5 years of age	Primary treatment phase: 52 weeks Total trial duration including extension treatment phase: Up to 209 weeks	Ongoing; CSR containing complete safety data and all available efficacy data from all 15 patients collected up to the data cut-off date of 28SEP2012

Type of Trial	Trial Identifier	Objective(s)	Trial Design and Type of Control	Dosing Regimen and Route of Administration	Number of Patients	Patient Population	Duration	Trial Status; Type of Report Submitted
Safety, Efficacy	MOR-008	Primary objective of the primary treatment phase: • To evaluate the safety of 2.0 and 4.0 mg/kg/week elosulfase alfa administered for 27 weeks Primary objective of the extension phase: • To evaluate the long-term safety of 2.0 and 4.0 mg/kg/week elosulfase alfa in patients with MPS IVA	Phase 2, Randomized, Double- Blind, Multicenter Trial	elosulfase alfa 2.0 mg/kg/week *or* 4.0 mg/kg/week 4 hour intravenous (IV) infusions	25 (enrolled)	MPS IVA patients age 7 years and older who are able to walk at least 200 meters in the 6MWT	Primary treatment phase: 27 weeks Total trial duration including extension treatment phase: Up to 157	Ongoing; CSR containing complete safety data from all 25 patients collected up to the data cut-off date of 14SEP2012

*Sponsor's Table, Module 5.2.

5.2 Review Strategy

The Phase 3 placebo-controlled trial, MOR-004, is the pivotal trial upon which evidence of substantial effectiveness is to be assessed. This Phase 3 trial and its extension trial MOR-005 are described in Section 5.3 Discussion of Individual Studies/Clinical Trials. The results of the primary and secondary efficacy endpoints from Trial MOR004, including the pharmacodynamic endpoint, are the focus of the discussion in Section 6 Review of Efficacy. The safety data from Trial MOR004 and the total exposed population are discussed in Section 7 Review of Safety.

5.3 Discussion of Individual Studies/Clinical Trials

Trial MOR004:

5.3.1 Trial Design, Objectives, Endpoints and Trial Population

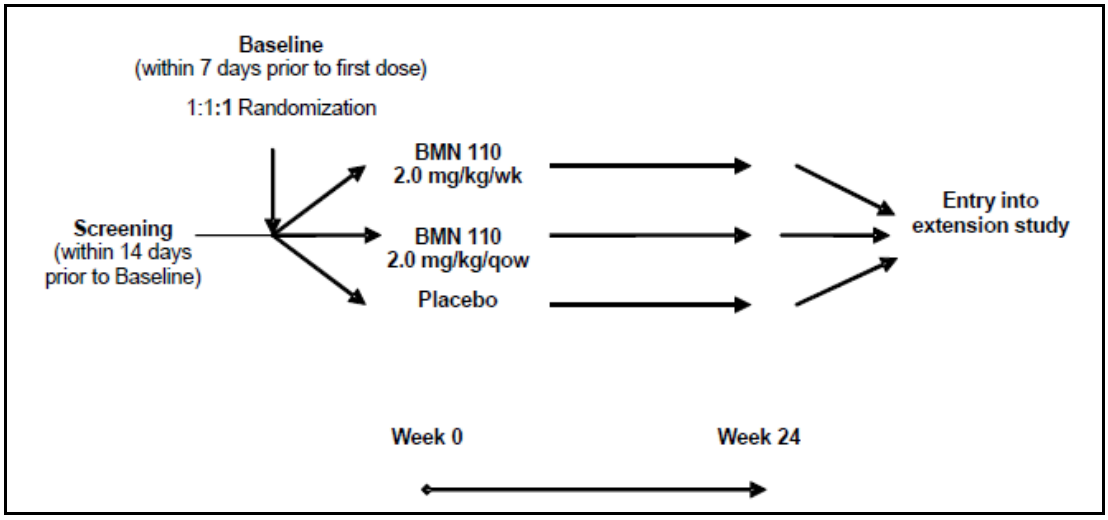
Trial Design:

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational trial of PK, efficacy, and safety
- Population: Patients with MPS IVA aged 5 years and older
- N = 177 randomized, 175 completed
- Treatment: 1:1:1 randomization
    - elosulfase alfa 2.0 mg/kg once per week (QW)
    - elosulfase alfa 2.0 mg/kg once every other week (QOW)
    - Placebo

  The randomization was stratified by screening 6MWT categories (≤200 meters and >200 meters) and age groups (5-11, 12-18, and ≥19 years old).

  Pretreatment with antihistamine was administered to all patients, while pretreatment with an antipyretic was permitted at Investigator discretion.
- Trial Duration: up to 27 weeks including a 2-week screening period, a 1-week baseline assessment period, and a 24-week treatment period (See Figure 1: Trial MOR004 Schema)
- Clinical sites: 33 sites in 17 countries including Argentina, Brazil, Canada, Colombia, Denmark, France, Germany, Italy, Japan, Portugal, Qatar, Saudi Arabia, South Korea, Taiwan, Netherlands, United Kingdom, and the United States

Figure 1: Trial MOR004 Schema



* BioMarin's Figure 8.1.1, CSR MOR004, p.71.

Objectives:

- Primary:
  - To evaluate the ability of elosulfase alfa to enhance endurance, as measured by increase in meters walked in the 6-minute walk test (6MWT) from baseline to Week 24.
- Secondary:
  - To evaluate the ability of elosulfase alfa to enhance endurance, as measured by increase in stairs climbed per minute in the 3-minute stair climb test (3MSCT) from baseline to Week 24.
  - To evaluate the ability of elosulfase alfa to reduce urine keratan sulfate (uKS) levels in patients with MPS IVA from baseline to Week 24.
- Tertiary:
  - To determine the pharmacokinetic (PK) parameters of 2.0 mg/kg/week elosulfase alfa and 2.0 mg/kg/every other week elosulfase alfa administered intravenously (IV).
  - To evaluate the ability of elosulfase alfa to improve respiratory function, as measured by the percent increase in pulmonary function tests (i.e., maximum voluntary ventilation (MVV), forced vital capacity (FVC), forced

expiratory volume in 1 second (FEV1), forced inspiratory vital capacity (FIVC), and forced expiratory time (FET)) from baseline to Week 24.

- To evaluate the effect of elosulfase alfa on:
  - biochemical markers of inflammation and bone and cartilage metabolism
  - quality of life as assessed by the MPS Health Assessment Questionnaire (MPS HAQ)
  - hearing as measured by audiometry
  - cardiac valve function as measured by echocardiogram (ECHO)
  - corneal clouding as assessed by physical examination

- Safety:
  - To evaluate the safety and tolerability of elosulfase alfa infusions, at doses of 2.0 mg/kg/week and 2.0 mg/kg/every other week, over a 24-week period

Endpoints:

- Primary: Change in 6MWT distance from baseline to Week 24
- Secondary: 1) Change in 3MSC rate from baseline to Week 24, 2) pharmacodynamic effect of Elosulfase alfa on the change in uKS levels from baseline to Week 24
- Tertiary: measurement of PK parameters, respiratory function, bone and cartilage metabolism biomarkers, quality of life, hearing, cardiac valve function, and corneal clouding were assessed
- Safety was assessed through adverse events (AE), concomitant medications and surgical procedures, vital signs, physical examinations, clinical laboratory testing (clinical chemistry, hematology, and urinalysis), 12-lead ECGs, ECHO, and monitoring of anti-idursulfase antibodies.

Trial Population

Inclusion Criteria:

- At least 5 years of age.
- Documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA.

- Willing and able to provide written, signed informed consent, or in patients under the age of 18 (or 16 years, depending on the region), able to provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the trial has been explained, and prior to any research-related procedures.
- Must have an average screening 6MWT distance ≥ 30 and ≤ 325 meters.
- Sexually active patients must be willing to use an acceptable method of contraception while participating in the trial.
- Females of childbearing potential must have a negative pregnancy test at screening and be willing to have additional pregnancy tests during the trial.

Exclusion Criteria:

- Previous hematopoietic stem cell transplant (HSCT).
- Previous treatment with elosulfase alfa.
- Has known hypersensitivity to any of the components of elosulfase alfa.
- Major surgery within 3 months prior to trial entry or planned major surgery during the 24-week treatment period.
- Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the trial.
- Use of any investigational product or investigational medical device within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments.
- Concurrent disease or condition, including but not limited to symptomatic cervical spine instability, clinically significant spinal cord compression, or severe cardiac disease that would interfere with trial participation or safety as determined by the Investigator.
- Any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the trial.

Medical Officer's Comment:

The objectives and trial population are appropriate.

5.3.2 Scheduled Study Procedures and Safety Assessments

All patients received a non-sedating antihistamine (cetirizine or loratadine) 30-60 minutes prior to infusion. Patients received a sedating antihistamine if they had prior infusion reaction or allergies to non-sedating antihistamine, but a similar proportion of

patients received sedating antihistamines across placebo and elosulfase alfa treatment groups.

Endurance assessments
All assessments were performed 5 days **prior** to infusion, or otherwise 2 days after infusion. Endurance tests (6MWT and 3MSC) were performed in duplicate, on separate days, at screening, Week 12, and Week 24. The two endurance tests were not performed on the same day, but in the following order: first 6MWT, first 3MSCT, second 6MWT, second 3MSCT. Test results were averaged to determine final measurement.

- For the 6MWT, patients were instructed to walk a straight, flat 30 meter course at their own pace, making turns at either end of the course, for 6 minutes in duration. Walk aids, such as braces, ankle-foot orthotics, splints, crutches, cane, or walker, were allowed but must be used consistently throughout the trial. If a walk aid was used during the Screening visit, the same walk aid had to be used for future assessments.
- For the 3MSC test, patients walked up stairs with a handrail that could be used for support for three minutes. The number of steps climbed was recorded.

Other Assessments

- Urine samples for urine KS and creatinine (measured from first voids) and blood samples for immunogenicity testing were collected at baseline, Weeks 2 and 4, and every 4 weeks thereafter.
- Radiographs of the cervical spine were taken at Screening to determine if endurance tests were contraindicated.
- Vital signs were measured before infusion (<30 minutes), every 30 minutes for the first hour of infusion, every hour for the remainder of infusion, and) after completion of infusion (<30 minutes).
- The Mucopolysaccharidosis (MPS) Health Assessment Questionnaire (HAQ) was completed by the patient or a parent/guardian for patients who are under 14 years of age at Screening, Week 12, and Week 24. The MPS HAQ is a 52-item questionnaire originally developed to assess the self-care and mobility skills of patients with MPS I. It has been modified for the MPS IVA patient population. The MPS HAQ assessed self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting) and mobility skills (dexterity, mobility, walking, stair climbing, ability to step on and off curbs, move >50 ft distances, and gross motor skills). The questionnaire also assessed the extent to which caregiver assistance was required in the performance of these activities.

The schedule for additional tertiary endpoints and the safety endpoints are described in Figure 2: Schedule of Assessments in Trial MOR004.

Figure 2: Schedule of Assessments in Trial MOR004

Assessments and Events	Screen	Baseline	Weeks 0 through 24																								
			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	2
Informed consent	X																										
Medical history and demographics	X																										
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight for purpose of drug preparation			X				X				X				X				X				X				
Physical examination	X														X												X
Audiometry examination		X																									X
Anthropometry examination		X																									X
6-Minute walk test	XX														XX												XX
3-Minute stair-climb test	XX														XX												XX
Respiratory function		X																									X
ECG	X																										X
ECHO	X																										X
Radiograph, cervical spine (flexion–extension)	X																										
Radiograph, lumbar spine		X																									
Radiograph, lower extremity[a]		X																									X
MPS Health Assessment Questionnaire		X													X												X
Clinical laboratory tests	X	X							X						X						X						X
Urine KS and creatinine		XX			X		X				X				X				X				X				X

Assessments and Events	Screen	Baseline	Weeks 0 through 24																								
			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	2
PK assessment			X																						X		
Blood inflammatory biomarkers		X													X												X
Blood biochemical markers, bone and cartilage metabolism		X													X												X
Thyroid panel	X														X												
Urine pregnancy test	X	X													X												X
Immunogenicity tests		X			X		X				X				X				X				X				X
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of study drug[b]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

* BioMarin Table 8.5.1.1, CSR MOR004, pp.84-85.

† ETV = early termination visit

[a] Radiographs of the lower extremity were performed only in patients younger than 20 years old

[b] Patients with a severe reaction associated with infusion or a reaction that required infusion interruption had an additional blood sample taken to assess C4, serum tryptase, total IgE, and drug-specific IgE levels. Samples for C4, serum tryptase, and total IgE were obtained shortly after cessation of the infusion. Since elosulfase alfa interferes with the IgE assay, a blood sample for drug-specific IgE was to be taken no sooner than 6 to 8 hours post infusion. A sample taken the day after the reaction was preferred but may not have been practical. If the sample was positive, the extra volume of serum was used to further characterize the drug-specific IgE assay.

An independent Data Monitoring Committee (DMC) reviewed AE data during the trial and an independent Allergic Reaction Review Board (ARRB) was available to review severe reactions associated with infusions during the trial.

5.3.3 Statistical Analysis

BioMarin planned to enroll approximately 162 patients (54 patients in each group) to achieve more than 90% power to detect a difference of 40 meters in mean change in the 6MWT between each of the elosulfase alfa treatment groups and the placebo group, assuming that the common standard deviation (SD) is 65 meters at an overall two-sided significance level (α) of 0.05 with the Hochberg method for multiplicity adjustment. The MOR-004 trial would be considered positive if both comparisons of the drug regimens to placebo render *p*-values less than 0.05 or the comparison of one of the drug regimens to placebo results in a *p*-value less than 0.025.

- Primary endpoint: The analysis was an Analysis of Covariance (ANCOVA) model of the change in 6MWT from baseline to Week 24, with treatment groups, baseline 6MWT categories (≤200 meters and >200 meters) and age groups (5-11, 12-18, and ≥19 years old) as factors. Each active treatment group was compared to the placebo group, and *p*-values were calculated. Least-squares (LS) estimated means and confidence intervals (CIs) for the treatment effects of each elosulfase alfa dose regimen compared with placebo were also calculated.

- Secondary endpoints: The same ANCOVA model analysis used for the primary endpoint was also used for the secondary endpoints 1) the change in 3MSCT from baseline to Week 24 and 2) the Week 24 percentage change from baseline in the normalized uKS measurement. Urine keratan sulfate (uKS) and urine creatinine (for normalization) were measured through quantitative laboratory analysis. The normalized uKS concentration to creatinine was calculated using the following formula:

  Normalized urine KS = urine KS / urine creatinine

5.3.4 Trial MOR004 Results

- Patient Demographics and Patient Disposition are discussed below in Sections 6.1.2 Demographics and 6.1.3 Patient Disposition, respectively.
- Pharmacokinetic results are discussed in Section 4.4.3 Pharmacokinetics.
- Results of the primary and secondary efficacy endpoints, including the pharmacodynamic endpoint (uKS), are the focus of the discussion in Section 6 Review of Efficacy.
- Safety results, together with safety data from the total exposed population are discussed in Section 7 Review of Safety.

5.3.5 Synopsis of Extension Trial MOR005

A phase 3, multicenter, multinational, two-part trial to evaluate long-term efficacy and safety of elosulfase alfa 2 mg/kg QW and elosulfase alfa 2 mg/kg QOW in MPS IVA patients. Of the 175 eligible patients completing Trial MOR004, 173 patients with aged 5 years and older enrolled in Trial MOR005 Part 1.

- Part 1, Double-blind, Duration 24 weeks

  Patients who received placebo in MOR004 were re-randomized (1:1) to one of the elosulfase alfa dosing regimens [2.0 mg/kg once per week (QW) or every other week (QOW)], and patients initially randomized to elosulfase alfa remained on their assigned dosing regimen. Therefore, the four treatment groups in Part 1 reflect doses received during both MOR004 and Part 1 of MOR005. See Table 6. Part 1 ended on November 30, 2012. The majority of patients rolled over into Part 2 (N=169).

Table 6: Patients per Treatment Group in Trials MOR004 and MOR005

MOR004		MOR005	
Treatment Group	**n**	**Treatment Group**	**n**
Placebo	58	Placebo -QOW	29
		Placebo-QW	29
QOW	59	QOW-QOW	59
QW	56	QW-QW	56

- Part 2, Open-label, Duration up to 216 weeks
  - Effective December 1, 2012, after completion of the final primary efficacy and safety analyses from MOR-004 and based on the recommendation of the Data Monitoring Committee (DMC), all patients enrolled in Part 2 of MOR005 began receiving elosulfase alfa 2.0 mg/kg QW. Data provided in Section 6 of this document summarizes both Part 1 and Part 2 as of the cutoff date January 3, 2013.
  - Per FDA request, an addendum to MOR005 Part 2 data with a cutoff date of September 3, 2013 was provided on September 27, 2013.

- Pretreatment with antihistamine was administered to all patients and pretreatment with an antipyretic was permitted at investigator's discretion.
- Duration: up to 240 weeks
- Clinical sites: 37 in 19 countries including United Kingdom, United States, France, Canada, Brazil, Columbia, Argentina, Denmark, Germany, Italy, Japan, Netherlands, Norway, Portugal, Qatar, Saudi Arabia, South Korea, Taiwan, and Turkey.

Study Procedures and Assessments were similar to MOR004; however, timing was less frequent for most assessment. For example, the endurance tests (6MWT, 3MSC) were conducted every 24 weeks instead of every 12 weeks.

- In Part 1, each patient completed safety and efficacy assessments every 12 weeks, including uKS normalized to creatinine, physical examination, clinical laboratory assessments, immunogenicity tests, and pregnancy testing (as appropriate). The 6MWT and the 3MSC were performed at Week 12 and Week 24, then at 24-week intervals thereafter. The anthropometric measurements, respiratory function tests, the MPS HAQ, audiometry examinations, and laboratory tests were performed every 24 weeks. The Patient Impression Questionnaire (PIQ) was completed 1 hour (±15 minutes) following the second 3MSCT at Baseline and at Week 24 to assess the patient's perceived impairment and improvement on performing the test.
- In Part 2, each patient has been completing safety and efficacy assessments every 24 weeks, including uKS normalized to creatinine, physical examination, clinical laboratory assessments, immunogenicity tests, and pregnancy testing (as appropriate). The MPS HAQ, anthropometric measurements, and laboratory tests are performed every 24 weeks. At selected sites, audiometry examinations are also performed every 24 weeks. Respiratory function tests, ECGs, echocardiogram, 6MWT, and 3MSC are performed every 48 weeks. Every 72 weeks (approximately every 18 months), patients undergo radiographs of the cervical spine, lumbar spine, and for patients ≤20 years of age, of the lower extremities.

The results of the efficacy and safety from Trial MOR005 are discussed in Section 6 Review of Efficacy and Section 7 Review of Safety.

6 Review of Efficacy

Efficacy Summary

BioMarin submitted one phase 3 clinical trial (MOR004) to support the effectiveness of elosulfase alfa (BMN 110) for treatment of patients with MPS IVA. This phase 3 trial compared two dosing regimens against placebo: elosulfase alfa 2 mg/kg weekly (QW)

and elosulfase alfa 2 mg/kg every other week (QOW). The primary endpoint was the change in distance walked in the six-minute walk test (6MWT) from baseline to Week 24. Patients in the QW treatment group demonstrated a statistically significant mean change in the 6MWT of 22.5 meters (p-value <0.05) when compared to placebo. Patients in the QOW treatment group performed similarly to those in the placebo group. The 23-meter difference between the QW and placebo groups is modest, and its clinical meaningfulness is not clear. The results of the secondary endpoint, the change in three-minute stair climb (3MSC) rate from baseline to Week 24, did not provide additional support to primary efficacy data. Neither the QW nor the QOW treatment group demonstrated a statistically significant change in the 3MSC. The QW treatment group had the most difference from placebo on the 3MSC, but the mean increase from baseline was 1.1 stairs per minute (p-value 0.49). The results of the pharmacodynamic endpoint (change in normalized uKS from baseline to Week 24) demonstrated a good response in both elosulfase alfa treatment groups. Patients in the QW treatment group experienced a mean reduction of 40% normalized uKS, while those in the QOW treatment group experienced a 30% reduction.

Subgroup analysis of the 6MWT demonstrated greater improvement in performance in patients who walked less than 200 meters on baseline 6MWT and received the QW dosing regimen than those who walked greater than 200 meters on the same dosing regimen. MPS IVA patients who were able to walk ≤ 200 meters at baseline on 6MWT climbed approximately 15-17 stairs per minute on baseline 3MSC and were more likely to use a walking aid. However, these same patients achieved a 40-meter improvement on the 6MWT when compared to the placebo group. Patients who walked more than 200 meters on baseline 6MWT achieved an 11-meter improvement on the 6MWT when compared to placebo. The subgroup of patients who walked ≤ 200 meters at baseline 6MWT were approximately four years older than those who walked > 200 meters at baseline. Additional subgroup analysis by age revealed that the more patients who walked ≤ 200 meters at baseline experienced the most benefit from treatment with the QW dosing regimen. Patients aged 12-18 years who received the QW dosing regimen performed the best on the 6MWT with a mean increase of 48 meters in 6MWT from baseline to Week 24, when compared to placebo.

Review of the long term efficacy data left uncertainty about the long term efficacy in this patient population. Patients who continued on the QW dosing regimen for another 48 weeks in the extension study (Trial MOR005) demonstrated no improvement on the 6MWT over what was demonstrated in the 24 weeks of Trial MOR004. Some improvement was seen in the 3MSC endpoint; however, its importance could not be determined due to lack of a placebo comparison group.

In summary, treatment with elosulfase alfa 2.0 mg/kg QW resulted in a modest yet statistically significant improvement on the 6MWT in MPS IVA patients after 24 weeks of treatment, with no worsening of 6MWT performance after 72 weeks of treatment. The 6MWT improvement was most remarkable amongst patients in the QW group who were

able to walk shorter distances at baseline. Concerns remain about long term durability of effect and patient immunogenicity status. Further evaluation of the clinical benefit of elosulfase alfa should be assessed through a clinical trial of longer duration, together with monitoring spontaneous immunologic tolerance to elosulfase alfa. In such a trial, secondary clinical outcome measures that may accurately assess changes in disease-specific symptoms and function of MPS IVA patients should be evaluated.

6.1 Indication

The proposed indication for elosulfase alfa is "For patients with Mucopolysaccharidosis Type IVA (MPS IVA; Morquio A syndrome)."

6.1.1 Methods

Background on Six-Minute Walk Test (6MWT)
The primary efficacy endpoint for Trial MOR004 is the change in distance walked in a six-minute walk test (6MWT). The 6MWT is a measure of submaximal exercise. The test measures the distance a person walks in six minutes. The walking course should be a straight, hard and flat surface, measuring 30 meters (100 ft) in length with turning room at either end. [13] The walker may go at his own pace, resting as needed, within the prescribed testing time. Normal ranges for six-minute walking distances (6MWD) in healthy adults range from 500-580 meters, with men walking slightly longer than women.[13] In a study by Geiger R *et al.* a modified 6MWT was used where the children utilized a measuring wheel for motivation. Healthy children, aged 3 to 11 years, walked from 492 to 667 meters, boys walking further than girls, and distance increasing with age and height.[14] In children and adolescents, age, height, and weight have been found to correlate significantly to 6MWD.[15]

Clinical Uses of 6MWT Assessment
BioMarin reports that the 6MWT may assess functional exercise capacity and mobility and is relevant to the activities of daily living. In the medical field, the 6MWT is used when an individual requires mobility aids or when a treadmill or cycle ergometer is not indicated for measuring cardiopulmonary fitness. It has been used to evaluate exercise capacity adults with chronic lung disease (e.g. COPD), congestive heart failure (CHF), and for monitoring mobility status in older persons. The 6MWD has been shown to be a strong predictor of morbidity and mortality in patients with primary pulmonary

13 ATS Statement: Guidelines for the Six-Minute Walk Test . Am J Respir Crit Care Med Vol 166. pp 111–117, 2002.
14 Geiger R, Strasak, A, Treml B, et al. Six minute walk test in children and adolescents. J Pediatr 2007; 150:395-399
15 Klepper SE, Muir N: Reference values on the 6-minute walk test for children living in the United States. Pediatr Phys Ther 2011, 23:32-40.

hypertension and CHF.[16,17] The 6MWT has been evaluated in COPD patients and found to be sensitive to commonly used therapies such as pulmonary rehabilitation, oxygen, long-term use of inhaled corticosteroids and lung volume reduction surgery. In a review of 6MWT in COPD adults by Rasekaba et al., a change in walking distance of 50-55 meters was considered clinically meaningful in most disease states.[18] However, longitudinal data in COPD patients demonstrated that 6MWD declines over time. Over a period of 5 years in patients with stage III COPD (FEV_1 30–50% predicted) the distance declined by 19% (an average of 16 m per year) and by 26% in patients with stage IV COPD (FEV_1 <30% predicted); however, deterioration in distance was independent of decline in FEV_1.

In CHF, the 6MWD has an inverse relationship with New York Heart Association (NYHA) functional class; however the test itself is less reliable to detect changes related to heart failure therapy. In patients with heart failure, the average 6MWD ranges from 310 m (left ventricular ejection fraction (LVEF) 20%) up to 427 m in those with mild disease (LVEF 53%). The European Society of Cardiology further describes that a 6MWD <300 m implies severe impairment and poor outcome, while a distance >500 m indicates moderately preserved exercise capacity and a low risk of clinical events.[19]

The 6MWT has been used to monitor independent mobility over time in older persons and identify those who are at risk of injury while crossing an intersection.[20] Crossing the typical 30-meter long intersection requires a minimum speed of 3.5 feet/second (64 meters/minute), whereas a threshold of 12 meters/minute predicted nursing home status.

6MWT Experience in Chronic Pediatric Conditions

The walk test has been administered in pediatric patients to evaluate chronic conditions such as juvenile idiopathic arthritis (JIA) and adolescent idiopathic scoliosis (AIS). In a small study of pediatric patients aged 7-17 years with JIA, a mean 6MWD of 545 ± 20.7 meters (range 392–688) was achieved.[11] This range of walking distance was similar to that of healthy elderly persons. The 6MWT was deemed to be a good measure of functional exercise capacity, however, it was demonstrated that test results varied by

16 Shah MR et al. Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. Am J Cardiol. 2001 Nov 1;88(9):987-93.
17 Miyamoto S et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2000 Feb;161(2 Pt 1):487-92.
18 Rasekaba, T et al. The six-minute walk test: a useful metric for the cardiopulmonary patient. The Intern Med J. 2009 Aug;39(8):495-501.
19 Metra, M et al. Advanced chronic heart failure: A position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2007 Jun-Jul;9(6-7):684-94. Epub 2007 May 3.
20 Noonan V, Dean E. Submaximal Exercise Testing: Clinical Application and Interpretation. Phys Ther. 2000 Aug; 80(8): 782-807.

patients' age, weight, and height. [21,22] In another study of 86 patients with AIS who were candidates for surgical treatment, a mean 6MWD of 434 ± 66 was achieved.[23] It should be noted that patients with cardiovascular, pulmonary, muscular and joint abnormalities were excluded from the study. Compared to the control group of healthy volunteers without spinal deformities, patients with AIS walked an average of 156 meters less, had a more rapid respiratory rate, had slightly lower oxygen saturation, and required more effort as measured by the Borg scale score (patient assessment of effort used to determine dyspnea). It was concluded that the 6MWT demonstrated the cardiorespiratory restrictions of AIS patients when compared to healthy controls.

The 6MWT has some limitations as an outcome measure in pediatric conditions. First, there is a wide range of variability in the test procedures despite guidelines provided by the American Thoracic Society specifying the procedure of conducting the 6MWT.[24] Second, the test is an effort-based exercise that is prone to bias. This is especially significant when attempting to engage a pediatric patient whose performance on the test could be influenced by their developmental stage, understanding and willingness to perform. Third, Bartels B et al. also points out that 6MWT results vary by chronic pediatric disease (i.e. cerebral palsy, cystic fibrosis, Duchenne Muscular Dystrophy, congenital heart disease, obesity, spina bifida) and should be interpreted with caution.[25] Bartels *et al*. recommends alternative outcome measures to be utilized to assist in interpreting clinical meaningfulness in each chronic disease population.

6MWT Experience in MPS Diseases

The 6MWT has been used in MPS drug development, including the pivotal trials of Aldurazyme (laronidase), an ERT for MPS I (Hurler's Syndrome). Table 7 - Reviewer's Table: Six Minute Walk Test Results from Clinical Trials for Other Mucopolysaccharidoses below summarizes the treatment differences reported for 6MWT in clinical trials for approved MPS disease treatment. For the Aldurazyme trial, an Advisory Committee was convened to evaluate the appropriateness of the 6-minute walk test to assess treatment benefit in patients with MPS I. The Committee members unanimously agreed that a 38 meter treatment effect was a meaningful treatment benefit in walking capacity for MPS I patients and recommended approval of Aldurazyme based.

21 Paap E, van der Net J, Helders PJM, Takken T. Physiologic response of the six-minute walk test in children with juvenile idiopathic arthritis. Arth Care Res 2005; 53:351-356.
22 Hassan J, van der Net J, Helders PJM, Prakken BJ, Takken T. Six minute walk test in children with chronic conditions. Br J Sports Med 2010; 44:270 - 274.
23 dos Santos Alves VL and Avanzi O. Objective Assessment Of The Cardiorespiratory Function Of Adolescents With Idiopathic Scoliosis Through The Six-Minute Walk Test. Spine 2009;34:E926–E929.
24 ATS Statement: Guidelines for the Six-Minute Walk Test . Am J Respir Crit Care Med Vol 166. pp 111–117, 2002.
25 Bartels B, de Groot JF, Terwee CB. The Six-Minute Walk Test in chronic pediatric conditions: a systematic review of measurement properties. Phys Ther. 2013;93:529–541

Table 7 - Reviewer's Table: Six Minute Walk Test Results from Clinical Trials for Other Mucopolysaccharidoses

Drug Name, Approval Year	Disease	Treatment difference between active and placebo for change from baseline 6MWT distance	Duration of Tx (weeks)
Aldurazyme 2003	MPS I; Hurlers	38 m (125 ft)	26
Naglazyme* 2005	MPS VI; Maroteaux-Lamy	92 m	24
Elaprase 2006	MPS II; Hunters	37 m	53

* In Naglazyme clinical trials, the walk test was administered over 12 minutes.

6MWT Assessment in MPS IVA Patients

BioMarin conducted a prospective longitudinal natural history study (MOR001) in 316 MPS IVA patients which showed that these patients are able to walk a mean distance of 212.6 ± 152.2 meters on the 6MWT at baseline (median distance 224 meters; range 0-864 meters).[26] Compared to the 6MWT distances of healthy children demonstrated in Geiger R *et al.* 2007, MPS IVA patients achieve a more limited walking distance. The walking ability of MPS IVA patients decreases with age, contrary to the increasing walking ability with age in healthy children. Table 8 (below) compares the mean 6MWT distances between healthy subjects and MPS IVA patients by age group.

Medical Officer Comment

Despite some limitations of the 6MWT, and lack of a better outcome measure, the 6MWT was found acceptable as the primary endpoint for the elosulfase alfa Phase 3 trial. The Phase 3 study population was selected because they were most likely to show change on the 6MWT. Study patients had to be able to walk at least 30 meters and no more than 325 meters. The upper limit of this inclusion criterion reflects the 75th percentile of 6MWT performance from the natural history study (Trial MOR001).

26 Harmatz P, Mengel KE, Giugliani R, et al. The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A patients. *Mol Genet Metab* 2013;109:54-61.

Table 8 – Reviewer's Table: Mean 6MWT Distance Comparison between Healthy Subjects and MPS IVA Patients

Age Group (years)	Mean 6MWT (meters)		Age Group (years)	Mean 6MWT (meters)	
	Healthy subjects [a]			Longitudinal study on MPS IVA patients [b]	MOR004 MPS IVA patients at baseline
	Male	Female			
3-5	537± 96	502 ± 90	0-4	252 ± 122	n/a
6-8	578 ± 56	573 ± 69	5-11	233 ± 140	229 ± 69
9-11	673 ± 62	662 ± 57			
12-15	698 ± 75	663 ± 51	12-18	181 ± 177	194 ± 77
≥16 y	726 ± 61	664 ± 50			
40-80 [c]	576 (399, 778) [d]	494 (310, 664) [d]	≥19	193 ± 149	169 ± 72

[a] Geiger R, Strasak, A, Treml B, et al. Six minute walk test in children and adolescents. *J Pediatr* 2007;150:395-9.
[b] Harmatz P, Mengel KE, Giugliani R, et al. The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A patients. *Mol Genet Metab* 2013;109:54-61.
[c] Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998;158:1384-7.
[d] Median (5^{th}, 95^{th} percentiles) is reported.

Background on Three-Minute Stair Climb (3MSC)

The secondary efficacy endpoint for Trial MOR004 was the change in number of stairs climbed per minute in the 3MSC test. In this test, patients walk up stairs that have a handrail for support, for three minutes. The 3MSC is used as a pre-operative stress test in patients who will undergo lung resection. Patients who are able to complete three to five flights demonstrate sufficient pulmonary reserve to be cleared for surgery. The 3MSC has a strong relationship to pulmonary function, but may also be an indicator of cardiovascular conditions (i.e. angina, claudication).[27] A small study by Pollock *et al.* in patients with chronic airway obstruction suggested that stair climbing may be a more demanding exercise than cycle ergometry.[28] However, similar to the 6MWT, the 3MSC is also influenced by patient motivation and cooperation.

BioMarin states that the 3MSC reflects "impairment in multiple organ systems including cardiopulmonary and musculoskeletal, and that the degree of strain put on the cardiopulmonary system during the 3MSC is significantly greater than during the 6MWT." They describe a study by Benn et al. where the circulatory demands in healthy, older males upon climbing three to four flights of stairs at a moderate pace (60-65 steps/min for approximately 50-70 seconds) peaked at a much more rapid rate than 10 minutes of horizontal walking at 2.5 mph intermittently carrying a 30-pound weight or

27 J W Bolton, D S Weiman, J L Haynes, C A Hornung, G N Olsen and C H Almond. Stair climbing as an indicator of pulmonary function. Chest 1987; 92: 783-788.
28 M Pollock, J Roa, J Benditt and B Celli. Estimation of ventilatory reserve by stair climbing. A study in patients with chronic airflow obstruction. Chest 1993; 104: 1378-1383.

4 minutes of walking up a moderately steep slope.[29] BioMarin further asserts that stair climbing may provide additional information about disease burden and functional status such that MPS patients with pre-existing joint pathology may not demonstrate improvement due to joint dysfunction, despite improvement in cardiorespiratory function.

6.1.2 Demographics

Patient Demographics

In Trial MOR004, the mean age was 15 years in both the placebo and elosulfase alfa 2.0 mg/kg/week treatment groups, and 13 years in the elosulfase alfa 2.0 mg/kg/every other week treatment group. The age of patients ranged from 5 to 57 years. Half of the study population consisted of patients aged 5 to 11 years. The majority of patients were White (59% to 75%), and Asians represented approximately one quarter of the trial population. There was a slight imbalance of patients by age groups (e.g. ages 5-11, 12-18, ≥19 years), race, and ethnicity. The placebo treatment group had a larger proportion of older patients (≥19 years), larger proportion of Whites, and fewer Asians compared to the elosulfase alfa treatment groups. With 55% female patients, the distribution of gender is balanced between the placebo and elosulfase alfa 2.0 mg/kg QW treatment groups. The 2mg/kg QOW treatment group had 42% female patients. Details of baseline demographics are provided below in Table 9.

Table 9: Baseline Patient Demographics (MOR004)

	Placebo (n = 59)	elosulfase alfa 2.0 mg/kg QOW (n = 59)	elosulfase alfa 2.0 mg/kg QW (n = 58)
Age at Enrollment (years)			
n	59	59	58
Mean (SD)	15.0 (11.30)	15.3 (10.79)	13.1 (8.10)
Median	11.9	12.0	11.1
Min , Max	5 , 57	5 , 49	5 , 42
Age Group (years)			
5 - 11	30 (50.8%)	31 (52.5%)	32 (55.2%)
12 - 18	15 (25.4%)	16 (27.1%)	16 (27.6%)
≥ 19	14 (23.7%)	12 (20.3%)	10 (17.2%)
Sex			
Female	32 (54.2%)	25 (42.4%)	32 (55.2%)
Male	27 (45.8%)	34 (57.6%)	26 (44.8%)

29 Benn SJ, McCartney N, McKelvie RS. Circulatory responses to weight lifting, walking, and stair climbing in older males. J Am Geriatr Soc. 1996 Feb;44(2):121-5.

Race			
Asian	11 (18.6%)	15 (25.4%)	14 (24.1%)
Black or African American	0	2 (3.4%)	2 (3.4%)
White	44 (74.6%)	35 (59.3%)	36 (62.1%)
Other	4 (6.8%)	7 (11.9%)	6 (10.3%)
Ethnicity			
Hispanic or Latino	13 (22.0%)	16 (27.1%)	9 (15.5%)
Not Hispanic or Latino	46 (78.0%)	43 (72.9%)	49 (84.5%)

* BioMarin's Table 10.2.1, CSR MOR004, p.133.

Treatment groups were also balanced for baseline characteristics and assessments such as medical history, baseline walk test categories, and 3MSC measurements. Patients receiving elosulfase alfa 2.0 mg/kg QW were slightly shorter in height than either of the placebo or the elosulfase alfa 2.0 mg/kg QOW treatment groups. Placebo patients had a slightly better mean 6MWT distance (212 meters) at baseline than either elosulfase alfa treatment groups (206 meters QOW and 204 meters QW). Approximately ~10% more patients used walking aids in the QOW treatment arm (27%) than either the placebo (19%) or the QW (16%) treatment groups. Details of baseline demographics are provided below in **Table 10**.

Table 10: Baseline Patient Characteristics (MOR004)

Parameter	Placebo n = 59	elosulfase alfa 2 mg/kg QOW n = 58	elosulfase alfa 2 mg/kg QW n = 58
Height (cm):			
Mean (SD)	105 (17)	105 (16)	101 (13)
Median (Min, Max)	100 (86, 165)	100 (81, 147)	99 (83, 141)
<3rd percentile-for-age	92%	88%	97%
Medical History:			
-Musculoskeletal disorders	81%	86%	79%
-Surgical/med procedures	73%	73%	67%
-Eye disorders	66%	66%	64%
-Cardiac disorders	51%	46%	47%
-Respiratory disorders	37%	48%	38%
Walking Aid Used†	11 (19%)	16 (27.1%)	9 (16%)
Walk Category			
≤200 m	23 (39.0%)	24 (40.7%)	23 (39.7%)
>200 m	36 (61.0%)	35 (59.3%)	35 (60.3%)
6MWT (m):			
Mean (SD)	211.9 (69.88)	205.7 (81.19)	203.9 (76.32)
Median (Min, Max)	229 (36, 312)	218 (47, 320)	217 (42, 322)
3MSC (stairs/min):			
Mean (SD)	30.0 (14.05)	27.1 (15.80)	29.6 (16.44)
Median (Min, Max)	31 (0, 59)	26 (0, 67)	31 (0, 72)

* Adapted from BioMarin's Table 10.2.2 and 10.2.3, CSR MOR004, pp.135 and 137.
† Patients used walkers, canes, or crutches.

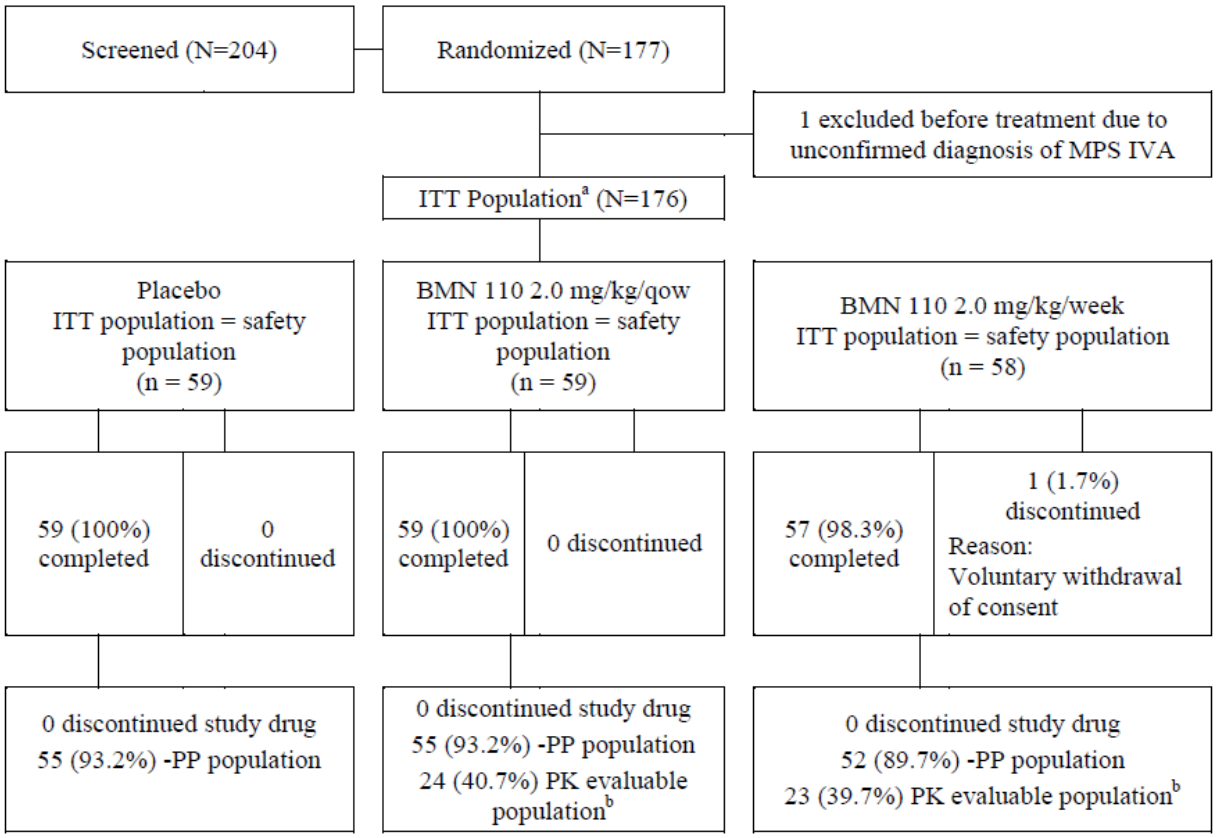
Medical Officer Comments:
The demographics and characteristics for the placebo and QW treatment groups were generally similar, with minor differences in age, race/ethnicity, and height. These minor differences did not translate into major differences of baseline 6MWT distances or 3MSC rates. The QOW group had a lower baseline 3MSC rate, which is related to its greater proportion of patients using walking aids. The QOW treatment group also had more male patients than either the placebo or QW groups. It is not clear that the different gender distribution in the QOW group had any impact on efficacy outcomes.

6.1.3 Patient Disposition

A total of 204 patients were screened and 177 were randomized. Of the 27 individuals who failed screening, 22 had a Screening 6MWT distance that exceeded the allowable

maximum of 325 meters, three withdrew the consent, and two were not randomized (reason unspecified). One randomized patient (Patient 1180-4161, placebo) was not dosed because the diagnosis of MPS IVA was not confirmed. Of the 176 patients in the ITT population, 59 were randomized to placebo, 59 to elosulfase alfa 2.0 mg/kg QOW, and 58 to elosulfase alfa 2.0 mg/kg QW. Of the 176 patients in the ITT population, 175 (99.4%) completed the trial, 1 (0.6%) discontinued the trial due to compliance concerns (Patient 0050-4090, elosulfase alfa 2.0 mg/kg QW). Patient disposition is displayed in Figure 3.

Figure 3: Patient Disposition (MOR004)



From BioMarin's Figure 9.1.1, CSR MOR004, p.127.

6.1.4 Analysis of Primary Endpoint(s)

Trial MOR004

The primary efficacy endpoint was the change in 6MWT distance (6MWD) from baseline to Week 24. Patients in the 2mg/kg once per week (QW) treatment group

demonstrated a mean increase of 37 meters in distance walked, while those in the 2 mg/kg once every other week (QOW) treatment group had a 15 meter increase which was comparable to the 14 meter increase in the placebo (Pbo) treatment group. The mean difference between the QW group and Pbo group was 23 meters, which was found to be statistically significant with a p-value <0.05. The mean difference between the QOW group and Pbo group was 0.5 meters and not statistically significant (p=0.9542). A treatment effect was, therefore, only demonstrated with the QW treatment group. Table 11 below displays the results of the primary endpoint analysis between the QW and Pbo treatment groups.

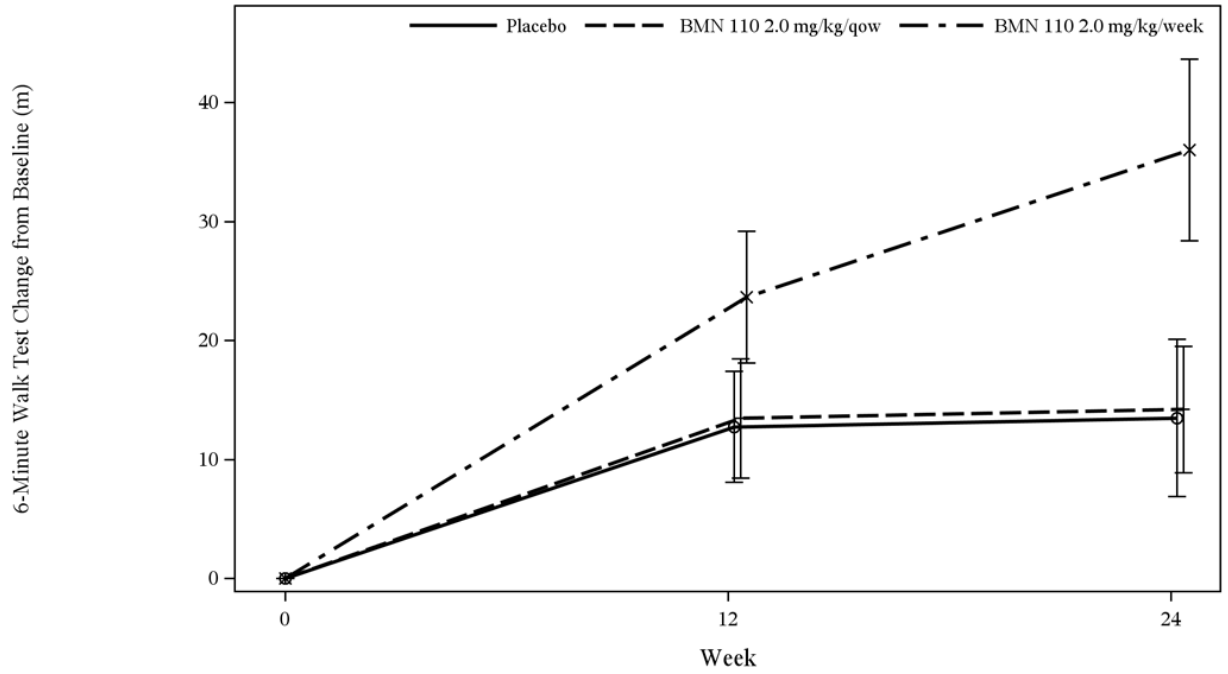
Table 11: Primary Endpoint – 6MWT Change from Baseline to Week 24 by Treatment Group (MOR-004)

	Placebo N = 59	**2 mg/kg QW n = 58**	**Treatment Effect† (QW-Placebo)**
Distance Walked, Change from Baseline to Week 24, meters			
Mean (SD) Median Min, Max 95% CI	14 (51) 10 -99, 221 0.6, 26	37 (58) 20 -58, 229 23, 50	22.5 m, 95% CI (4.0, 40.9) p = 0.0174
Percent Change from Baseline to Week 24 (%)			
Mean (SD) Median Min , Max 95% CI Limit	8.7 (28.83) 3.8 -45.6 , 105.4 -0.0 , 17.5	23.8 (44.43) 10.3 -38.7 , 257.9 15.0 , 32.9	14.9% 95% CI (2.7, 27.2) (exploratory analysis)

* From BioMarin's Table 10.4.1.1.1.1, CSR MOR004, p.145.
† ANCOVA model (primary end point analysis), adjusted for baseline covariates: age group and baseline 6MWT category

A graphical presentation of the primary efficacy analysis, shown in Figure 4, demonstrates the lack of difference between the QOW and Pbo groups. However, the difference between the QW and Pbo groups is more evident, without overlapping of confidence intervals.

Figure 4: Mean Change in 6MWT Distance (MOR004)



*BioMarin's Figure 14.2.1.4 from CSR MOR004, p. 611.

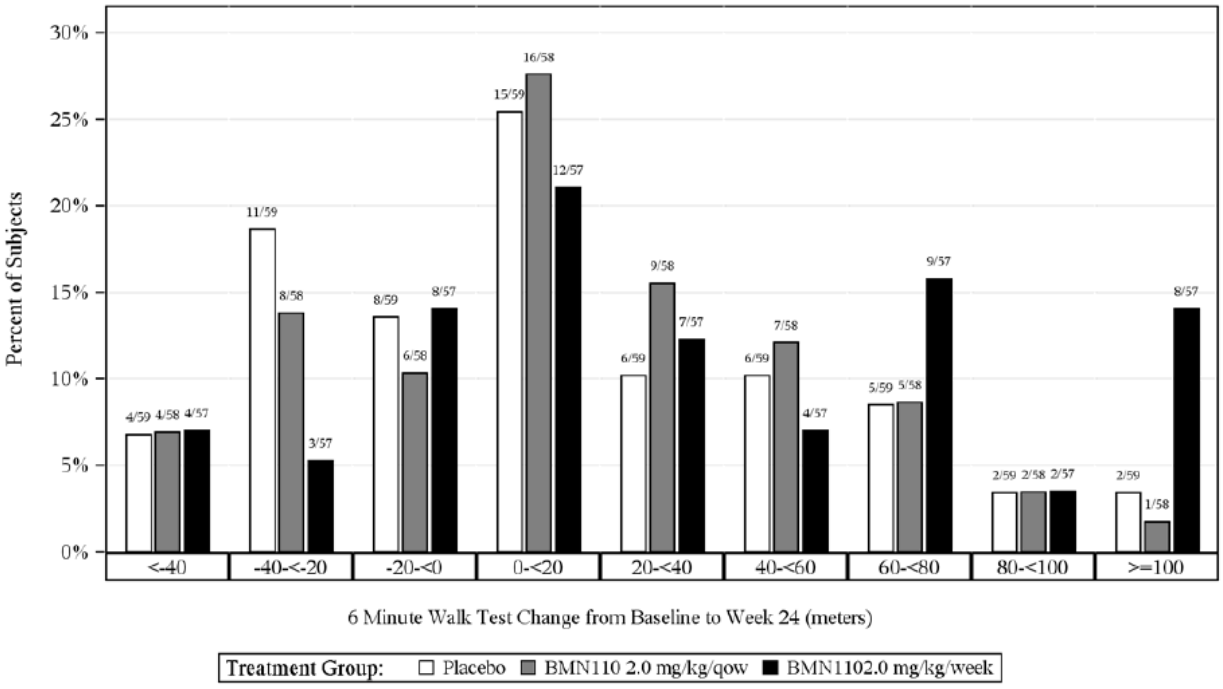
Medical Officer's Comment:
While the treatment effect between the QW and Pbo treatment group is statistically significant for the primary efficacy endpoint, the magnitude of improvement is modest and its clinical meaningfulness in the MPS IVA patient population is not clear.

The Division held a teleconference with patient caregivers and an adult patient in order to better understand the personal experiences of MPA IVA patients. During the teleconference, the most common symptoms reported by MPS IVA patients were fatigue, decreased exercise endurance (inability to change classes that are approximately 50 ft apart), joint stiffness, and pain. Patient and patient caregivers wished to see a drug that could improve the endurance and breathing, as well as resolve the short stature. This reviewer considers the 6MWT relevant to the MPS IVA population in that it reflects functional limitations in activities of daily living, but the clinical meaningfulness of the 6MWT improvement needs to be further explored.

Figure 5 shows that when the change in 6MWT from baseline to Week 24 was compared according to baseline 6MWT ability, the distribution was similar between the QOW and Pbo groups. The QW group, however, displayed two peaks of high

performing patients: those who achieved an increase of ≥ 60 meters but less than 80 meters and those who achieved ≥100 meters in 6MWD.

Figure 5: Distribution of Change from Baseline in 6MWT Distance



*BioMarin's Figure 14.2.1.10, from CSR MOR004, p. 635.

The eight patients in the QW group who achieved ≥100 m change in 6MWT at Week 24 were evaluated for characteristics that may have contributed to their performance. All eight were pediatric patients, with the mean age of 11±5 years and the median age of 9 years (range 5 to 18 years). Other demographics mirrored those of the total study population with similar distribution for race, gender, height, and use of a walk aid. Disease-related manifestations in their medical history were comparable to the overall study population for musculoskeletal disorders, respiratory disorders, and surgical and medical procedures. A slightly smaller proportion had cardiac disorders (38%) and eye disorders (50%), compared to ~48% and ~65% in the overall study population, respectively. [See Table 10.] These characteristics of the eight patients in the QW group who achieved ≥100 m change in 6MWT at Week 24 do not explain the better performance on the 6MWT.

A closer evaluation of their individual performance on 6MWT showed that patients who walked a shorter distance at baseline experienced the greatest percent change in

6MWD. In other words, the 6MWD at Week 24 was inversely related to 6MWD at baseline. This inverse relationship is also demonstrated throughout the larger study population. The eight QW patients' 3MSC rate at baseline did not correlate with the baseline 6MWT. The percent change in 3MSC rate at Week 24 appeared to be inversely related to 3MSC rate at baseline. It is noted that the two patients using walkers had the lowest baseline 3MSC rate. The performance of the eight QW patients on 6MWT and 3MSC are displayed in Table 12.

Table 12 - Reviewer's Table: 6MWT and 3MSCT Performance in Patients Who Received Elosulfase alfa 2 mg/kg QW and Improved in 6MWT by >100 meters from Baseline to Week 24 (MOR-004)

Patient ID	Age (years)	Baseline 6MWT (meters)	Change in 6MWT from Baseline to Week 24 (meters)	Baseline 3MSCT (stairs/min)	Change in 3MSCT from Baseline to Week 24 (stairs/min)
1180-4136	5.1	281	119	40	13
0090-4057	14.8	250	102	37	16
0025-4013	8.1	243	114	72	7
1235-4060	18.4	240	114	31	18
0050-4063*	9.5	189	140	17	18
1073-4111*	16.6	146	194	4	10
1017-4075	8.4	120	131	22	2
1024-4033	5.3	88	236	31	9

*patients used walker or walking frame

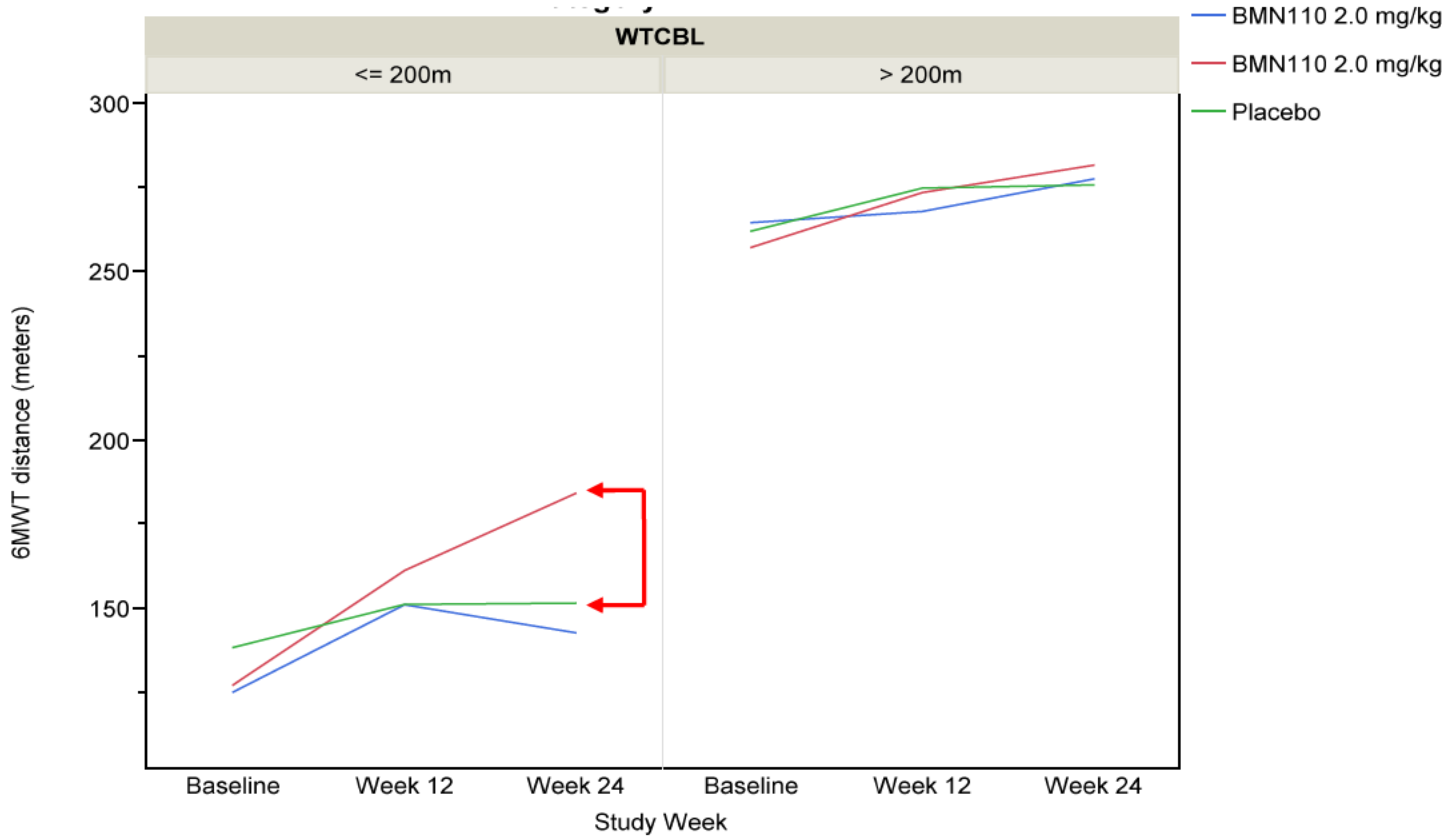
When the change in 6MWD is evaluated by baseline 6MWT performance in the overall study population, the pattern is consistent with that demonstrated in the eight high performing patients. The patients with smaller baseline 6MWD (≤ 200 meters) had greater improvement in walking abilities than those who walked > 200 meters at baseline. The patients who walked ≤ 200 meters at baseline seem to have driven the treatment effect for the QW group. The mean change from baseline in 6MWD in this group was 40 meters compared to 11 meters in the > 200 meter baseline 6MWD group. This is displayed below in both Table 13 and Figure 6.

Table 13: 6MWT Distance Walked by Baseline Walk Test Category -- Change from Baseline to Week 24

Subgroup	Parameter	Placebo N = 59	2 mg/kg QW n = 58
Baseline 6MWD ≤200m	N	23	23
	Mean (SD)	13 (39)	53 (67)
	Median	11	35
	Min, Max	-43, 95	-58, 229
	95% CI	-8, 35	32, 75
Baseline 6MWD >200m	N	36	35
	Mean (SD)	14 (57)	25 (49)
	Median	9	14
	Min, Max	-99, 220	-51, 119
	95% CI	-2, 30	8, 41

*From BioMarin's Tables 14.2.1.26 and 14.2.1.28, CSR MOR004.

Figure 6: Reviewer's Figure: 6MWT Distance by Study Week, Baseline Walk Test Category, and Treatment Group (MOR004)



The study patients who walked ≤ 200 meters at baselines were evaluated for characteristics that may have contributed to their performance. The age of the patients who walked ≤ 200 m was about four years older than those who walked > 200 m at baseline. Other demographic and clinical characteristics, such as gender, race, and height, were similar. The use of a walking aid was more common among the ≤200 m group, with 31 (44%) patients using a walker, cane or crutches. These 31 patients using walking aids were similarly distributed in the Pbo and QW treatment group, with slightly more in the QOW treatment group. Only five of 106 patients in the >200 m group used a walking aid and none were assigned to the QW treatment group. Patients who walked ≤ 200 m were more likely to have a positive medical history for surgical/medical procedures and respiratory disorders than those who walked >200 m. Table 14 further details these similarities and differences in the study population by baseline walking ability.

Table 14 – Reviewer's Table: Patients Characteristics by Baseline Walk Test Category

	Baseline Walk Test Category	
Parameters	**≤ 200 m**	**>200 m**
n	71	106
Age: Mean (SD) Median (Range)	 17 (10) 14 (5-47)	 13 (10) 10 (5-57)
Gender = Male	34 (48%)	54 (51%)
Race: White Asian Black Other	 51 (72%) 11 (15%) 2 (3%) 7 (10%)	 64 (60%) 30 (28%) 2 (2%) 10 (9%)
Height: Mean (SD) Median (Range) <3rd percentile 3rd- 10th percentile >50th percentile Not available	 102 (15) 99 (88-165) 62 (87%) 1 (1%) 0 8 (11%)	 105 (15) 101 (81-147) 100 (94%) 5 (4%) 1 (1%) 0
Walking Aid Used	31 (44%)	5 (5%)
Medical Hx: -Musculoskeletal disorders -Surgical/med procedures -Eye disorders -Cardiac disorders -Respiratory disorders	 57 (80%) 58 (82%) 48 (68%) 36 (51%) 38 (54%)	 86 (81%) 66 (62%) 65 (61%) 47 (44%) 32 (30%)

Medical Officer's Comment

A more remarkable change in 6MWD is seen in the MPS IVA patients who walked ≤ 200 meters on the baseline 6MWT. These patients underwent more surgical/medical procedures, had more respiratory issues and were on average four years older than those patients walking more than 200 meters at baseline 6MWT. This suggests that maximum clinical benefit may not be reserved only for the very young – as theorized for prevention of severe disease development in studies of other MPS diseases. The improvement of 6MWD demonstrated in the MPS IVA patients who walked ≤ 200 m on baseline 6MWT is appreciated as treatment benefit, although some interpretability issues remain without a supportive secondary efficacy endpoint.

Delphi Panel of Experts Responder Definition and Post Hoc Analysis of 6MWT Results

In order to define a minimal clinically important difference (MCID) in the 6MWT, BioMarin sought advice from experts in MPS IVA treatment through the Delphi process. The Delphi process involved two rounds of anonymous communication that surveyed opinions via a questionnaire and a final in-person consensus meeting. Nine experts reached consensus on the following responder definitions in MPS IVA patients who walked 30 to 325 meters at baseline.

Delphi Panel's Responder Definitions: [30]

- The overall study population should have a 15% change in 6MWD from baseline to Week 24
- For specific baseline 6MWD,
  - 20% change in 6MWD for patients with baseline 6MWD 30m to <100m
  - 15% change in 6MWD for patients with baseline 6MWD 100m to <200m
  - 10% change in 6MWD for patients with baseline 6MWD 200m to 325m

The Week 24 data from the Pbo and QW treatment groups was evaluated to determine how many patients would meet the Delphi responder definitions. When the 15% change in 6MWD was used as a responder definition for overall study population, 31% of Pbo group patients were considered responders, while 46% of QW group patients were considered responders. There were a similar proportion of responders in each treatment group when the responder definition was based on specific baseline 6MWD. Table 15 details these results of the Delphi responder definitions.

30 Hendriksz, CJ, Al-Jawad, M, Berger, KI, Hawley, SM et. al. Clinical overview and treatment options for nonskeletal manifestations of mucopolysaccharidosis type IVA. J Inherit Metab Dis . 2012.

Table 15: Results of Post-Hoc Analysis Using Delphi Responder Definitions*

	Placebo N=59	QW N=58
Overall 15% change from BL to Week 24 in 6MWT	18/59 (31%)	26/57 (46%)
Responder definition based on baseline 6MWT levels	20/59 (34%)	27/57 (47%)

*From BioMarin's Tables 14.2.1.53 and 14.2.1.56, CSR MOR004, pp. 810 and 813.

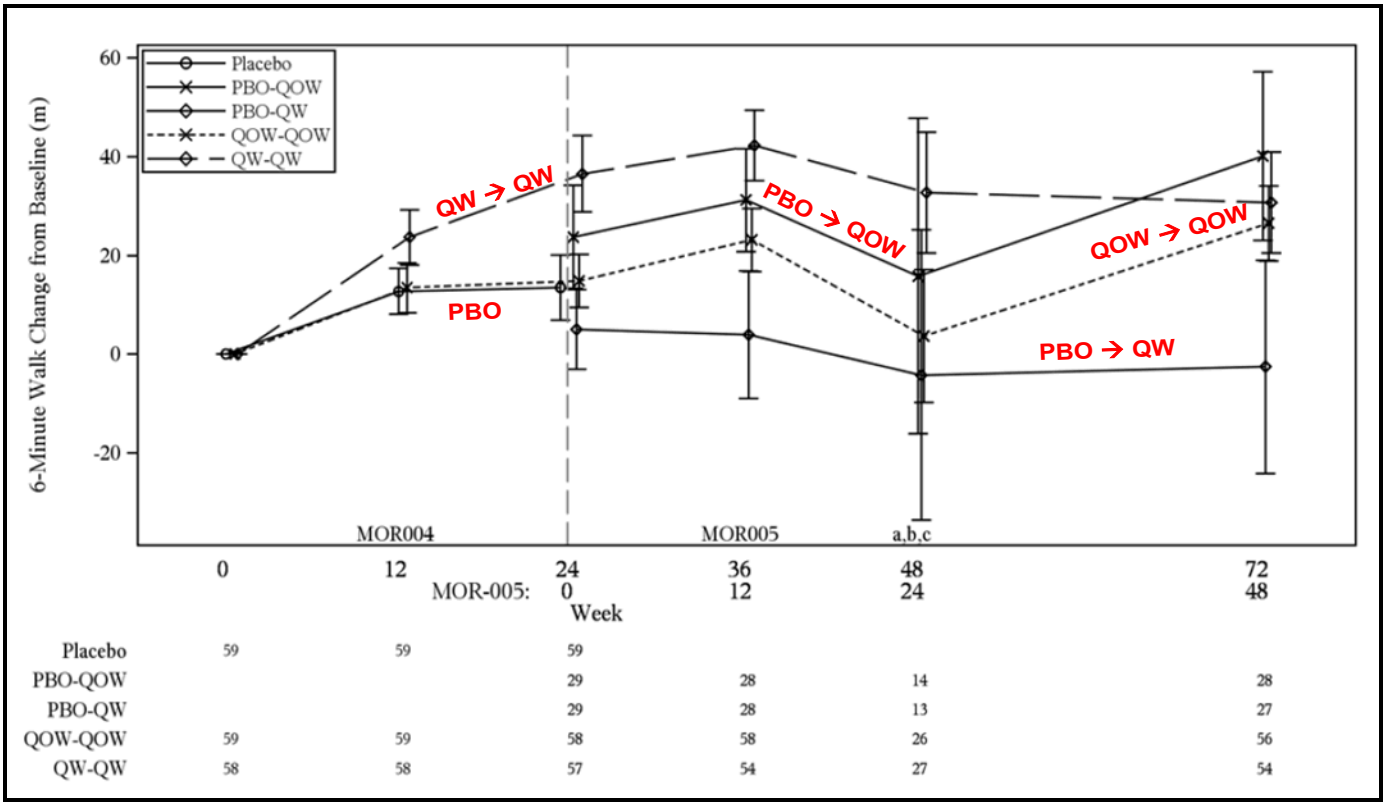
Medical Officer's Comment

The analysis of the change in 6MWD from baseline to Week 24 based on the Delphi responder definition was exploratory; however, the Delphi responder definitions appear to be consistent with literature findings. BioMarin describes that the percent change from baseline in the 6MWT yielded results consistent with the 10%-14% range in published studies. The Delphi responder definition also reflects the inverse relationship between the degree of 6MWT improvement and the baseline 6MWT performance. A greater percentage of improvement was expected with patients who walked less at baseline. Despite these conceptual concurrences, the proportion of patients meeting the Delphi responder definition is concerning. This reviewer does not appreciate a remarkable difference in the number of responders in the Pbo treatment group compared to the QW treatment group. Furthermore, less than half of the patients in the QW group were "responders". This exploratory analysis has limited value in demonstrating worthwhile clinical benefit in this population.

MOR005 Extension Trial

Patients who remained on QW treatment for an additional 24 weeks (n=56) in the extension trial (QW-QW treatment group) achieved a peak increase in mean 6MWD of 42 meters at Week 12 (a total of 36 weeks on drug). By Week 24 of the extension trial (total 48 weeks on drug), the mean change in 6MWD for the QW-QW group decreased back to 33 meters, a similar level that was attained after 24 weeks of treatment in MOR004 (i.e., mean change of 37 meters). No further increase in 6MWD is appreciated for the QW-QW group after 72 weeks of treatment. Figure 7 displays the mean change in 6MWD for all treatment groups during Trial MOR004 and the first 48 weeks of Trial MOR005.

Figure 7: Mean Change in 6MWT for MOR004 and Extension Trial MOR005



* BioMarin's Figure 14.2.1.1, September 27, 2013 Information Request Information, p. 221. Data reflected through September 3, 2013 cutoff date. At week 72 of treatment, 168 patients had received at least one dose of elosulfase alfa 2 mg/kg/week treatment in Part 2 of MOR005.

The drop in mean 6MWD for the QW-QW treatment group after 48 weeks of treatment is concerning and may be explained by a 50% reduction in number of patients assessed at that timepoint. The contribution of data from patients' 6MWD post orthopedic surgeries was also considered. The graph in Figure 7 includes post orthopedic surgery data (intent-to-treat population). Patients were asked to delay surgery during the MOR004 protocol, until the start of the MOR005 protocol. Therefore, any musculoskeletal limitations experienced during recovery from surgery may impact the mean 6MWD in Trial MOR005. Twenty-two patients had orthopedic surgery during MOR004 (n=2) and MOR005 (n=2); four in the QW-QW treatment group, eight in the QOW-QOW treatment group, four in the Pbo-QOW treatment group, and six in the Pbo-QW treatment group. The patients who had orthopedic surgery are listed in the table below.

Table 16: Reviewer's Table: Listing of Patients with Orthopedic Surgery in Trial MOR004 and MOR005

Treatment Group	Patient ID	Study Period
QW-QW	1167-4054	MOR005 Part 2
	0121-4139	MOR005 Part 2
	0050-4063	MOR005 Part 1
	0021-4003	MOR005 Part 1
QOW-QOW	1167-4037	MOR005 Part 1
	0121-4001	MOR005 Part 1
	0119-4080	MOR005 Part 1
	0050-4062	MOR005 Part 1
	0025-4035	MOR005 Part 2
	0024-4167	MOR005 Part 2
	0020-4144	MOR005 Part 2
	0018-4040	MOR005 Part 2
PBO-QW	1167-4059	MOR005 Part 1
	0287-4088	MOR004
	0109-4026	MOR005 Part 1
	0090-4056	MOR005 Part 1
	0021-4002	MOR005 Part 1
	0020-4143	MOR005 Part 2
PBO-QOW	0287-4110	MOR005 Part 2
	1075-4012	MOR004
	0109-4028	MOR005 Part 1
	0020-4142	MOR005 Part 2

* From BioMarin's Patient Listing 16.2.3.1, September 27, 2013 Information Request Information.

When post orthopedic surgery data is excluded from Figure 7 (modification not shown), the 6MWT results demonstrate that the QW-QW treatment group's performance was not impacted. The QOW-QOW treatment group's mean change in 6MWD at Week 48 is about 10 meters greater when post orthopedic surgery data is excluded. The large variability of 6MWT results for the placebo-switch treatment groups makes it difficult to draw any conclusions from the data. Therefore, the inclusion of post orthopedic surgical 6MWD does not explain the decrease in mean 6MWD for the QW-QW treatment group after 48 weeks of treatment.

Medical Officer's Comment

The 6MWT results of patients treated with QW dosing in Trial MOR005 are similar to the results seen in Trial MOR004. This reviewer has concern that, despite the ongoing MOR005 trial, the number of patients and the quality of data collected may not be sufficient to assess improved long term efficacy of elosulfase alfa in the MPS IVA population. Over time, patients will continue to have progressive

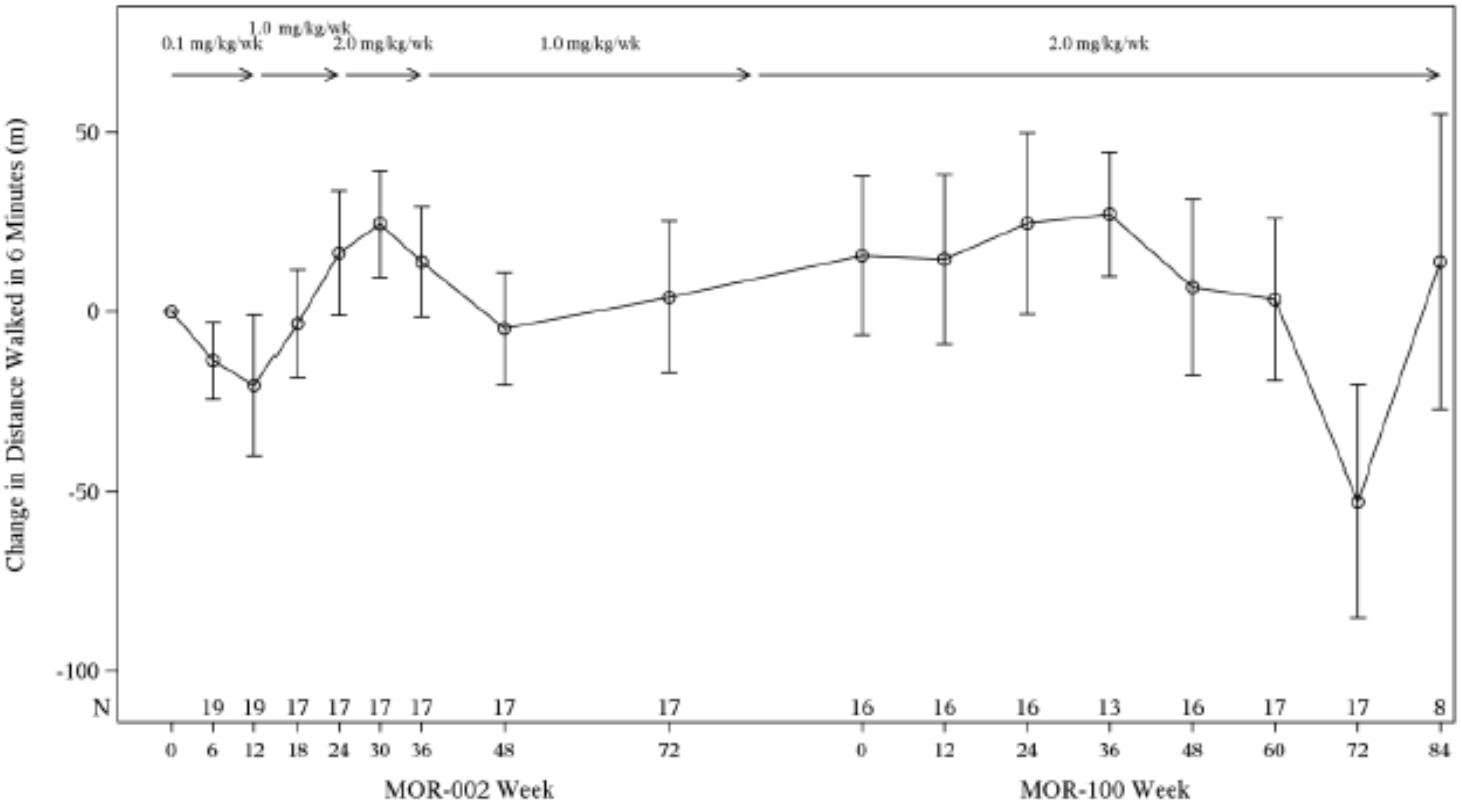
skeletal deformity and require orthopedic surgery, both of which will impact patient performances on 6MWT and 3MSC measurements.

The patients who completed placebo treatment in Trial MOR004, and switched to QOW or QW treatment in the extension trial, were not re-randomized using the strata of age and baseline walk test category. At weeks 48 and 72 of treatment, the Pbo-QOW group achieved a mean change in 6MWD from MOR-004 Baseline of 41 (±77) and 40 (±91) meters, respectively. The PBO-QW group achieved a mean change in 6MWD from MOR-004 Baseline of 15 (±84) meters at week 48 of treatment, but declined to -2.5 (±112) at week 72. These results suggest that the Pbo-QW group's performance on 6MWT did not change regardless of treatment, placebo or elosulfase alfa 2 mg/kg once per week. BioMarin remarks that the results from the placebo switched patients during Trial MOR005 are difficult to interpret and reflect the impact of unbalanced variables. BioMarin further reports that the results for the Pbo-QW group may be further skewed by patients with lower limb fracture (n=1) and orthopedic surgeries (see Table 16).

Medical Officer's Comment
Because BioMarin reported that placebo switched patients were not re-randomized in MOR005 based on age and baseline walk test category strata, a review of the baseline characteristics of MOR005 placebo switched patients for age, gender, and baseline 6MWT distance category was conducted. Both placebo switch treatment groups for Trial MOR005 were balanced for proportion of patients in each baseline 6MWT distance category. This distribution was also similar to that of the QW-QW and QOW-QOW treatment groups. However, age distribution found older patients in the PBO-QOW group (mean 17±14 years-old) than the PBO-QW (mean 14 ± 8 years-old). Gender distribution was also unbalanced between these groups; the PBO-QW group had less male patients (38%) than the PBO-QOW group (52%). The differences in age and gender in the placebo switched patient groups does not appear to justify the lack of improvement in the PbO-QW patients.

Phase 1/2 Trials MOR002 and MOR100
A more substantial drop in mean change in 6MWD was seen in the 17 patients who completed the Phase 1/2 open-label, dose-finding trial (MOR002) and enrolled in the extension trial (MOR100). In MOR100, patients achieved a peak change in 6MWD of 27 meters at treatment week 36, but experienced a major drop in 6MWD at Week 48 and Week 60 to mean values of 7m and 3m, respectively. BioMarin reports that these results were greatly impacted by four patients who required orthopedic surgery prior to the week 72 assessments. In three of these four patients, the Week 72 6WMD was approximately half of that measured at Week 60. The fourth patient had made much less progress on rehabilitation. Figure 8 displays the mean change in 6MWD in Trials MOR002 and MOR100 by study week and elosulfase alfa dose.

Figure 8: Mean Change from Baseline in 6MWT Distance by Study Week (MOR002/MOR100)



*BioMarin's Figure 6.4.2.1, CSR MOR100, p.60.

6.1.5 Analysis of Secondary Endpoints(s)

Three-minute Stair Climb (3MSC)

Trial MOR004

In Trial MOR 004, the secondary efficacy endpoint was the change in 3MSC from baseline to Week 24. As shown in Table 17, patients in all treatment groups performed similarly. Patients in the QW treatment group demonstrated the most difference from placebo, with a mean change of 1.1 stairs/min, CI95 (-2.1, 4.4), p-value =0.4935. Patients in the QOW treatment group performed similarly on the 3MSC to those receiving placebo with a change of -0.5 stairs/min, CI95 (-3.7, 2.8), p-value =0.7783.

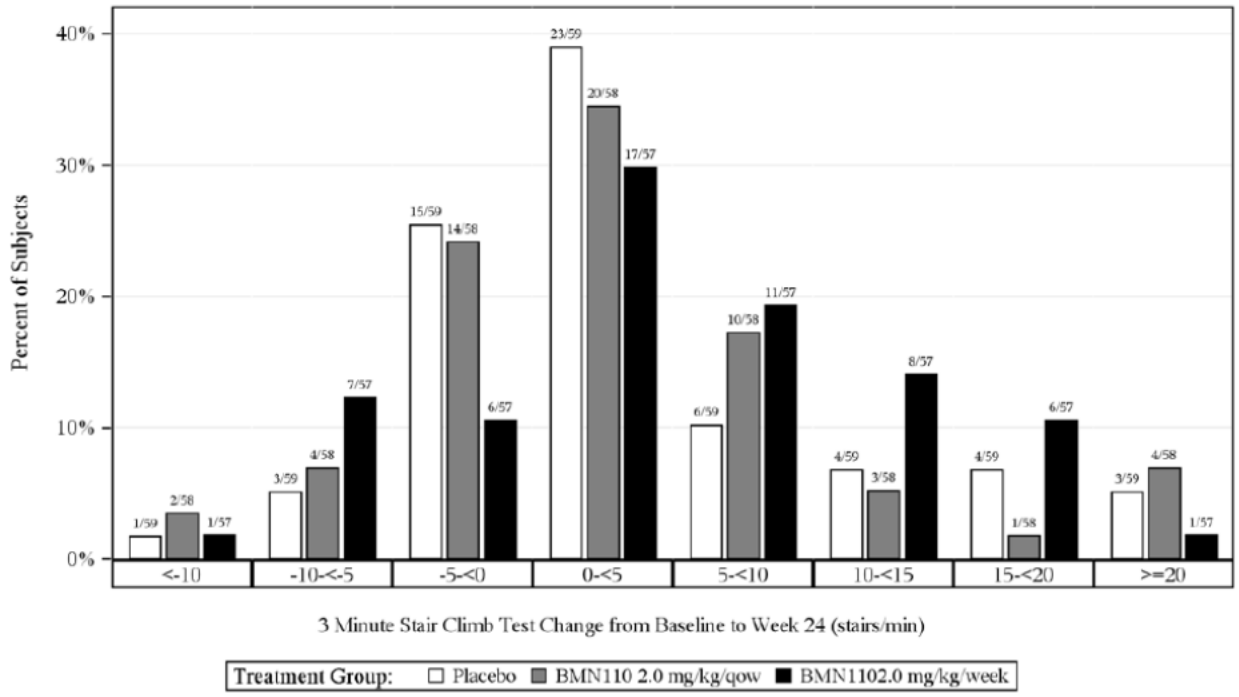
Table 17: Secondary Endpoint – Mean Change in 3MSC Rate (stairs/min) from Baseline to Week 24 by Treatment Group (MOR-004)*

Parameter	Placebo N = 59	2 mg/kg QOW n = 58	2 mg/kg QW n = 57
Mean (SD)	4 (9)	3 (10)	5 (8)
Median	1	2	4
Min, Max	-13, 33	-19, 46	-12, 21
95% CI	1, 6	1,6	2, 7

*From BioMarin's Table 14.2.2.8, CSR MOR004, p. 854.

When the proportion of patients achieving a similar level of change in 3MSC rate is compared by treatment group, there is no subgroup that is remarkable. Patients in the Pbo and QOW treatment groups had the greatest proportion of patients with ± 5 stairs/min 3MSC change, while the QW treated patients were more distributed on the side of positive increase in 3MSC rate. A grossly bell-shaped distribution is demonstrated by treatment group on the bar graph in Figure 9.

Figure 9: Distribution of Change from Baseline in 3MSC Rate*



*BioMarin's Figure 14.2.2.10 from CSR MOR004, p. 867.

When the change in 3MSC rate is evaluated by baseline 6MWT category, there is a striking difference in stair-climbing ability. Those who walked ≤ 200 meters at baseline (n=71) climbed stairs at 15-20 stairs/minute, while the patients who walked >200 meters at baseline (n=106) climbed stairs at approximately 35-43 stairs/minute. Despite these

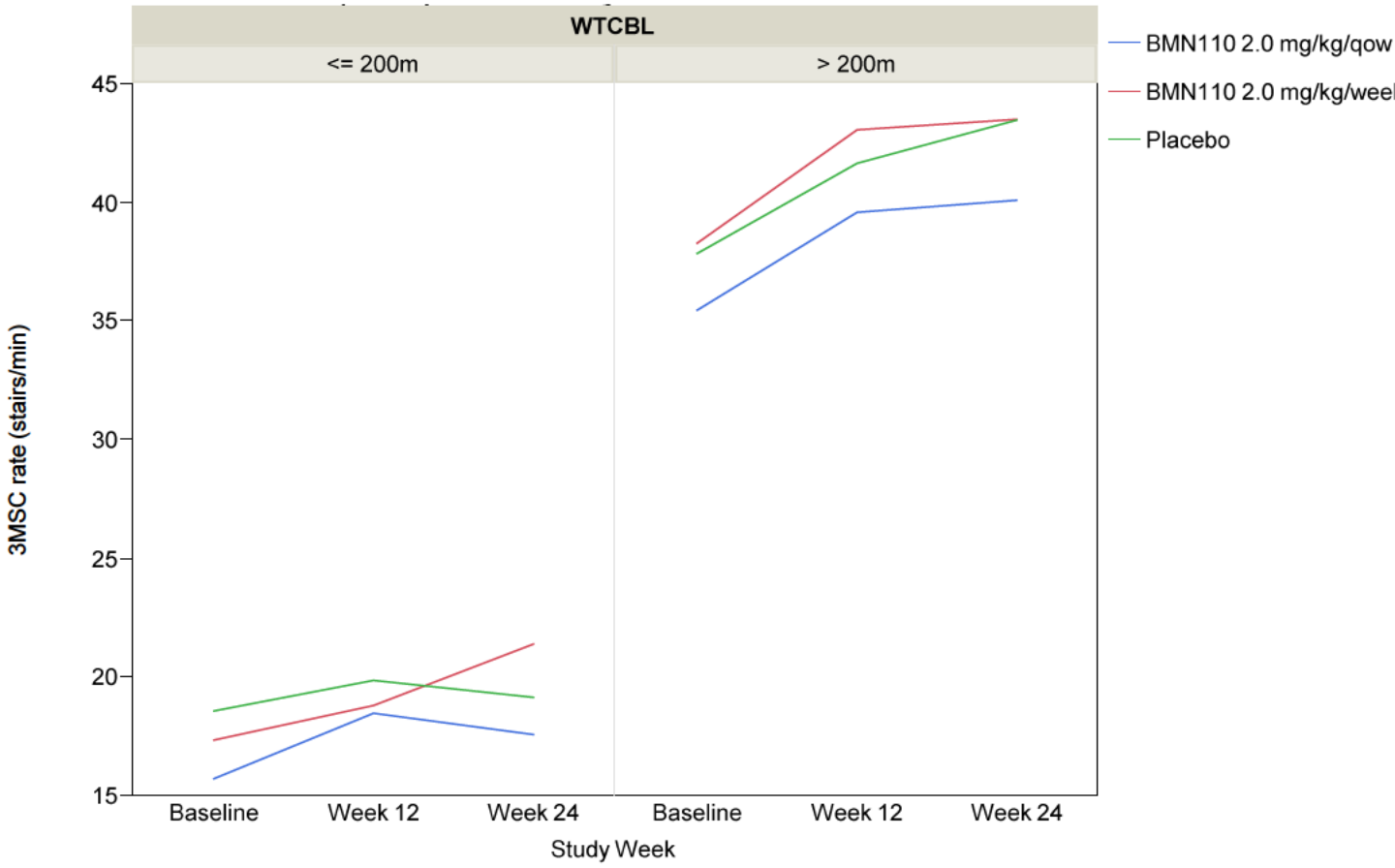
differences by baseline 6MWT category, there is still no remarkable difference between patients who walked ≤ 200 meters at baseline in the placebo group (median 3MSC rate 20 stairs/min) and those in the QW treatment group (median 3MSC rate 19 stairs/min). The 3MSC rates by treatment group and baseline 6MWT category are shown in Table 18.

Table 18: Reviewer's Table: 3MSC Rate by Treatment Group (MOR004)

	3MSC Rate (stairs/minute)								
	Placebo			QOW			QW		
Baseline 6MWT category	**n**	**Mean (SD)**	**Median (Min, Max)**	**n**	**Mean (SD)**	**Median (Min, Max)**	**n**	**Mean (SD)**	**Median (Min, Max)**
≤200 m	23	19 (9)	20 (0, 33)	24	18 (11)	17 (0, 46)	23	21 (14)	19 (0, 49)
>200 m	36	43 (17)	42 (0, 84)	35	40 (16)	39 (14, 79)	35	44 (15)	40 (19, 83)

Figure 10 demonstrates the mean 3MSC rate by study week, baseline walk test category, and treatment group.

Figure 10: Reviewer's Figure: Mean 3MSC Rate by Study Week, Baseline Walk Test Category, and Treatment Group (MOR004)



The Delphi panel of experts also recommended a responder definition for the 3MWC after 24 weeks of drug treatment: 20% change in 3MSC rate for patients who could climb stairs at baseline. Similar to the analysis of the 6MWD, 25% of the patients in the Pbo treatment group were responders, and 46% of the patients in the QW treatment group were responders.

Table 19: Results of Post-Hoc Analysis Using Delphi Responder Definitions*

	Placebo N=59	**QW N=58**
3MSC Overall 20% change from BL	15/59 (25%)	26/57 (46%)

*Adapted from BioMarin's Tables 14.2.1.54, CSR MOR004, p. 811.

Medical Officer's Comment

In past clinical trials of therapies intended to treat MPS, the 3MSC test was supportive of a treatment effect seen in the primary endpoint. The 3MSC test usually demonstrated a trend towards improvement or a statistically significant change at the end of the treatment period. However, this is not the case with Trial MOR004. The results of the 3MSC test are neither statistically nor clinically meaningful. All three treatment groups performed similarly on this secondary endpoint. This reviewer does agree that the 3MSC test may be more physically taxing for patients than the 6MWT; however, this does not explain why both patients who walked ≤ 200 meters and > 200 meters at baseline failed to have any appreciable gain with elosulfase alfa treatment. It is, perhaps, that the disease manifestations affecting hip flexion and knee articulation in MPS IVA may be such that elosulfase alfa treatment is unable to change them or the 3MSC test is not an appropriate measure to assess the small magnitude of change. A different efficacy measure such as range of motion or sequential radiographic imaging of the joints may be more informative. Alternatively, more time on treatment or a higher dose may be needed to demonstrate treatment effect on the 3MSC.

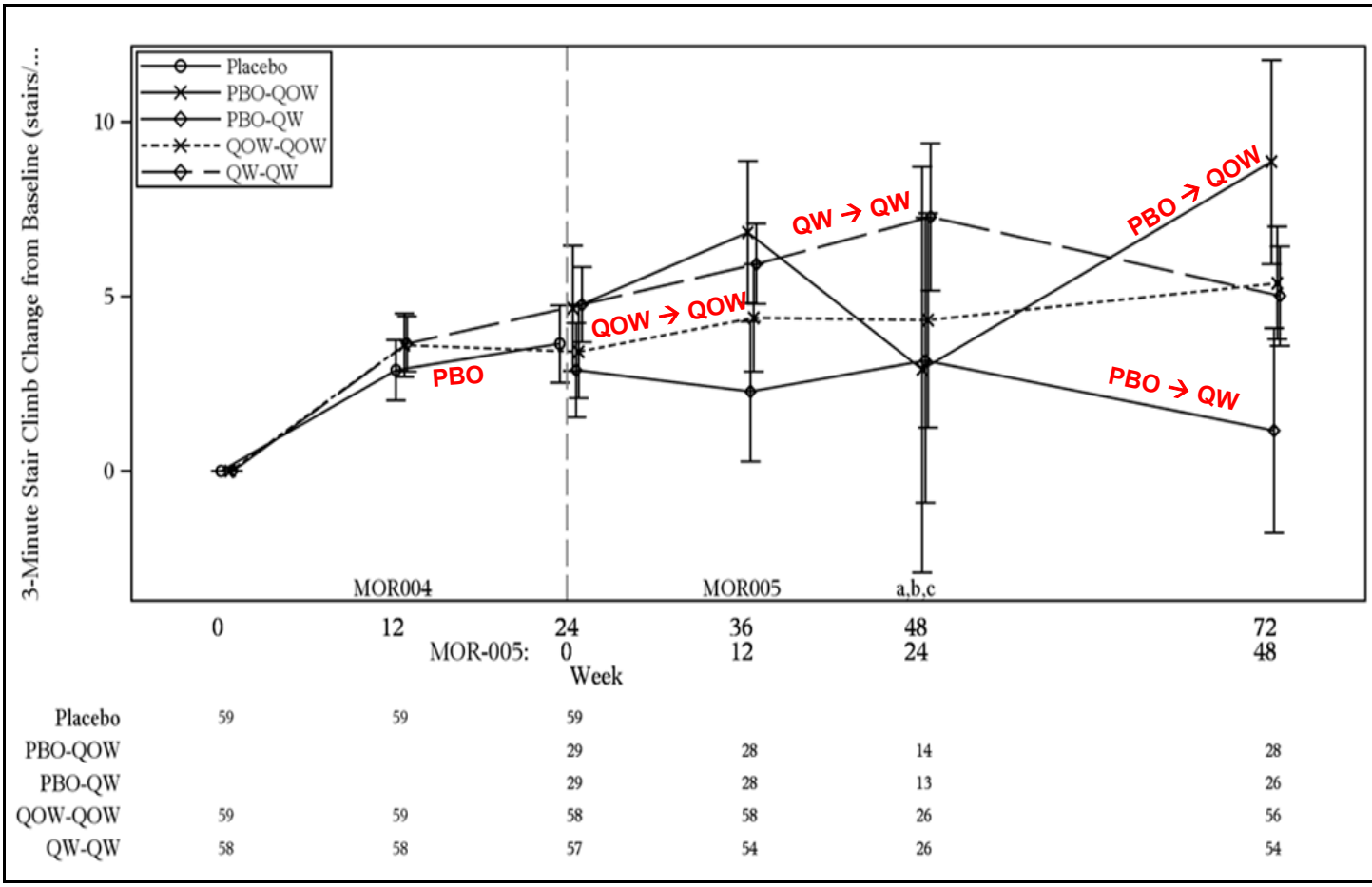
Trial MOR005

In contrast to the 6MWT results in Trial MOR004, the mean change in 3MSC rate in QW-QW patients slowly increased over the first 24 weeks of MOR005, with a mean change from week 0 to week 24 of 7 ±11 stairs/minute (total 48 weeks on treatment). This mean change in 3MSC rate declined, however, to 5 ±10 stairs/minute after a total of 72 weeks on treatment. This 3MSC rate is the same as that after 24 weeks of treatment in Trial MOR004. Figure 11 (below) displays the mean change in 3MSC rate for all four treatment groups during Trials MOR004 and MOR005. Again, the placebo switch groups are difficult to interpret.

Medical Officer's Comment

The results of the 3MSC in patients continuously treated with QW-QW dosing in Trial MOR005 suggests that no further significant changes in 3MSC rate are demonstrated over time. The change demonstrated during the first 24 weeks of Trial MOR005 is difficult to qualify as an important demonstration of efficacy because Trial MOR005 is an open-label trial design and the study population completing the 3MSC at this timepoint was reduced by approximately half.

Figure 11: Mean Change in 3MSC Rate for MOR004 and MOR005*



* BioMarin's Figure 14.2.2.1, September 27, 2013 Information Request Information, p. 225. Data reflected through September 3, 2013 cutoff date. At week 72 of treatment, 168 patients had received at least one dose of elosulfase alfa 2 mg/kg/week treatment in Part 2 of MOR005.

Urinary Keratan Sulfate (uKS) Excretion Level

In Trial MOR 004, the secondary endpoint of change in normalized uKS levels from baseline to Week 24 was a pharmacodynamic measure. The normalized uKS levels decreased in both QOW and QW treatment groups by 30% and 41%, respectively. The normalized uKS reductions achieved statistical significance for both groups. The normalized uKS levels dropped early (by Week 4) in the elosulfase alfa treatment groups and remained lower than the placebo group for the trial duration. Table 20 details the mean percent change in normalized uKS when compared to the placebo group.

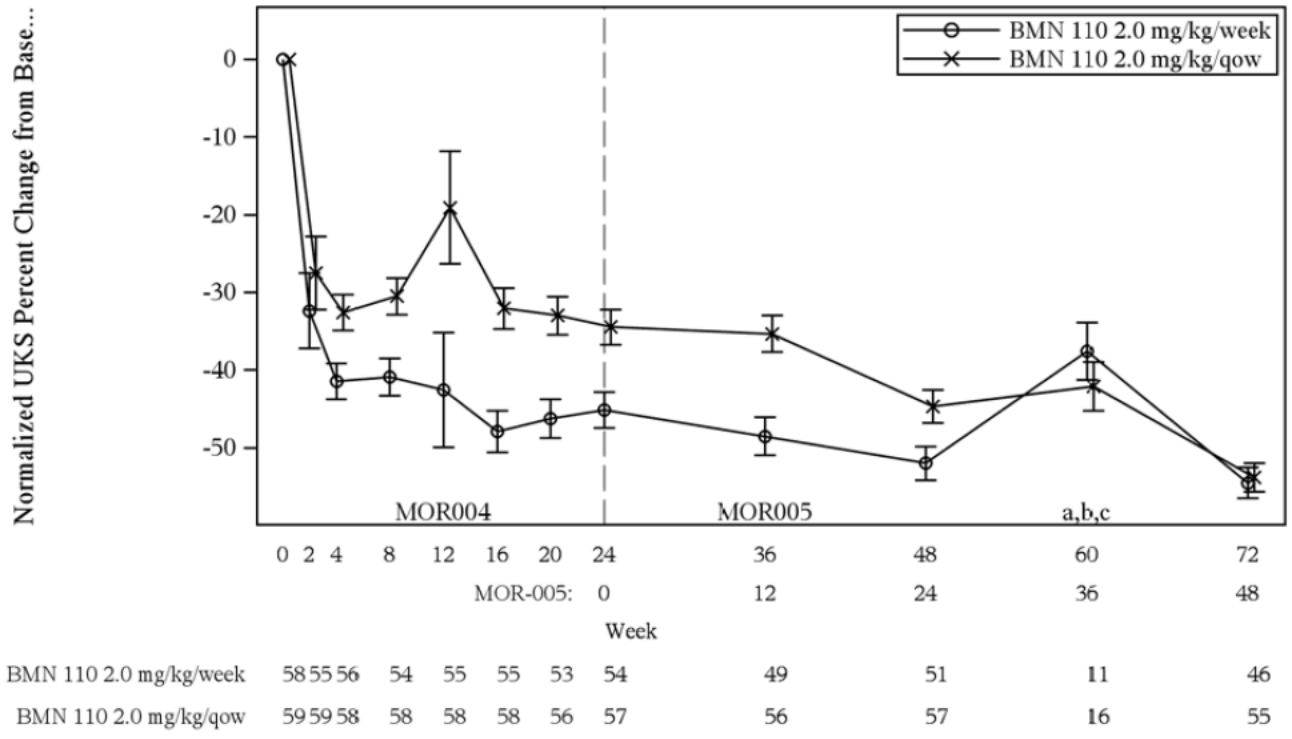
Table 20: Mean Change in Normalized Urine Keratan Sulfate from Baseline to Week 24 When Compared to Placebo (MOR-004)

Parameter	2 mg/kg QOW n = 59	2 mg/kg QW n = 58
Mean Percent Change	-30.2%	-40.7%
95% CI	-38.5, -22.0	-49.0, -32.4
	P<0.0001	P<0.0001

From BioMarin's Table 14.2.3.45, CSR MOR004, p.1487.

In Trial MOR005, the uKS levels continued to decline through Week 72 in patients receiving elosulfase alfa 2 mg/kg QW. This is demonstrated in Figure 12 below.

Figure 12: Mean Percent Change in Normalized Urine Keratan Sulfate (MOR004 and MOR005 through Week 48)*



* BioMarin's Figure 1.3.3.1, September 27, 2013 Information Request Information, p. 13. Data reflected through September 3, 2013 cutoff date. At week 72 of treatment, 168 patients had received at least one dose of elosulfase alfa 2 mg/kg/week treatment in Part 2 of MOR005.

Medical Officer's Comments
It is noted that the reduction in uKS does not correlate with the changes seen in the 6MWT performance. This is consistent with prior clinical trials of MPS disease therapies where a 50% or more reduction in urinary glycosaminoglycan excretion did not correlate with clinical efficacy outcomes.

6.1.6 Other Endpoints

Trial MOR004
There were multiple tertiary endpoints explored in Trial MOR004; however, no clinically important change was seen in the majority of these endpoints by Week 24 of the trial. Tertiary endpoints are as follows:

- pulmonary function tests:
  - forced vital capacity (FVC)
  - forced expiratory volume in 1 second (FEV_1)
  - maximum voluntary ventilation (MVV)
  - forced inspiratory vital capacity (FIVC)
  - forced expiratory time (FET)
- MPS Health Assessment Questionnaire
- blood inflammatory biomarkers
- blood biochemical markers of bone and cartilage metabolism
- anthropometric measurements (standing height, length, sitting height, and weight)
- skeletal radiographs of lumbar spine and lower extremity (lower extremity radiographs only in patients ≤ 20 years of age)
- audiometry examinations
- echocardiogram
- corneal clouding

For the tertiary endpoints of MVV and MPS HAQ wheelchair use, there were small differences that are discussed below.

Maximum Voluntary Ventilation
The maximum voluntary ventilation showed a minor change by Week 24, although not clinically significant. This section focuses on the tertiary endpoint of change in maximum voluntary ventilation (MVV) from baseline to Week 24. MVV is a measure of the maximum breathing capacity; the greatest volume of gas that can be inhaled and exhaled per minute by voluntary effort.[31] The patient usually performs the test for 12 seconds, and then the result is extrapolated to one minute. At week 24, both elosulfase alfa treatment groups had mean increases in MVV of 1.5 L/min compared to 0.5 L/min

31 Definition provided by The Free Dictionary by Farlex. Accessed September 3, 2013.

in the Pbo treatment group. Due to high variability between patients, the percent change in MVV from baseline to Week 24 was used for primary analysis. Mean percent change at Week 24 was 2.4% (± 21) for Pbo, 6.1% (±24) for the QOW group, and 10.8% (± 26) for the QW group. Table 21 summarizes the results of key pulmonary function tests, including maximum voluntary ventilation (MVV), forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1).

Table 21: Pulmonary Function Test Results (MVV, FEV_1, and FVC) by Treatment Group (MOR-004)

	Placebo N = 59	2 mg/kg QOW n = 59	2 mg/kg QW n = 58	Treatment Effect (QW-Placebo)
MVV (L/min) at baseline Mean (SD) Median (Min, Max)	35 (27) 27 (7, 129)	33 (20) 27 (10, 91)	28 (17) 25 (5, 76)	Mean difference (SD): **8.4%** (4.4%)
% Change in MVV from baseline to Wk 24 Mean (SD) Median (Min, Max)	**2.4%** (21) 0.5% (-40, 90)	**6.1%** (24) 3.5% (-33, 112)	**10.8%** (26) 7.2% (-43, 93)	
FVC (L) at baseline Mean (SD) Median (Min, Max)	1.2 (0.9) 0.9 (0.3, 5)	1.1 (0.7) 0.9 (0.3, 3)	0.9 (0.5) 0.8 (0.3, 3)	Mean difference (SD): **3.4%** (2.4%)
% Change in FVC from baseline to Wk 24 Mean (SD) Median (Min, Max)	**1.5%** (14) 0% (-31, 39)	**4.1%** (12) 2.3% (-18, 36)	**4.9%** (12) 3.3% (-19, 54)	
FEV_1 (L) at baseline Mean (SD) Median (Min, Max)	1.0 (0.7) 0.8 (0.3, 3.8)	0.9 (0.52) 0.8 (0.3, 2.6)	0.8 (0.4) 0.7 (0.3, 2.5)	Mean difference (SD): **2.9%** (2.7%)
% Change in FEV_1 from baseline to Wk 24 Mean (SD) Median (Min, Max)	**2.5%** (16.8) -2.2% (-26, 76)	**3.3%** (13.4) 4.0 (-43, 42)	**5.4%** (11.5) 5% (-17, 39)	

From BioMarin's Tables 10.4.1.3.1.1.1, 10.4.1.4.1.2.1 and 14.2.6.3, CSR MOR004.

The Delphi panel also proposed a responder definition for MVV at 20% change from baseline. In exploratory analysis, a higher proportion of responders were in the QW treatment group (29%, n=17) and QOW treatment group (21%, n=12) than in the Pbo group (12%, n=7).

Analyses of Pulmonary Function Tests (FVC, FEV, MVV) in relation to the Primary Endpoint in Trial MOR004

There are no standards exist to reliably estimate predicted pulmonary function values in the MPS IVA population due to their early growth arrest and short stature. However, using the results of spirometry, BioMarin conducted additional analyses of pulmonary function tests (FVC, FEV, MVV) in relation to the primary endpoint in Trial MOR004. The results of the correlation analyses of baseline PFTs and the change from baseline to Week 24 in 6MWT distance revealed weak relationships between these parameters. The following table shows the correlation coefficients (r) by treatment group.

Table 22: Correlation Analyses between Baseline Pulmonary Function Tests and the Change from Baseline to Week 24 in 6MWT Distance (MOR004)

Treatment Group	FVC and 6MWT r	FEV and 6MWT r	MVV and 6MWT r
All	-0.05	-0.04	-0.07
Placebo	-0.06	-0.05	-0.14
QOW	0.12	0.14	0.17
QW	-0.09	-0.09	-0.13

From Figure 1.2, 1.3, and 1.4 of BioMarin's Response to October 18, 2013 FDA Request.

Analysis of patients by degree of obstructive lung disease and change from baseline to Week 24 in 6MWT distance did not demonstrate a difference in treatment effect.

Trial MOR005

Continued treatment with elosulfase alfa for an additional 24 weeks led to further improvement in MVV in the QOW-QOW group but not the QW-QW group. The ANCOVA modeled mean percent changes after 48 weeks of treatment found an increase of 18% (CI95, 8.2, 27.3) and 2.3% (CI95, -8.4, 13.0) for the QOW-QOW and QW-QW groups, respectively

Medical Officer's Comment

While the MVV results at Week 24 of Trial MOR004 are statistically significant and there appears to be a dose-response with MVV, the clinical importance of this change is not clear. Few patients achieve a response. The change in MVV may be confounded since MVV is influenced by patient effort, coordination, neuromuscular disease, and airway obstruction. The MPS IVA patient population also has variable presentation of compromised respiratory function. The greatest change in MVV was seen in the 5 to 11 year-old age group.

MVV is approximately equal to FEV_1 x 40.[32] FEV_1 results in this trial demonstrated small positive changes in both QOW and QW treatment groups.

MPS Health Assessment Questionnaire (HAQ)

To further demonstrate the clinical relevance of improvements in efficacy measures, BioMarin reports additional analyses of individual MPS HAQ results from Trial MOR004. Although the numbers are small, results show that more subjects on QW treatment, compared to placebo, were able to perform important activities of daily living. The most important change was that no patients in the QW treatment group started to use a wheelchair by Week 24 compared to five patients in the placebo group. Figure 13 demonstrates this change in wheelchair use and other quality of life items.

Figure 13: Change in Individual MPS HAQ Items (MOR004)

From Figure 103.6, BioMarin's Response to October 18, 2013 FDA Request.

Medical Officer's Comment

While change in wheelchair use amongst placebo patients compared to the QW treatment group is informative, there is limited value to the changes seen on the MPS HAQ. The questionnaire was originally designed for the MPS I population and has not been validated for measurement of MPS IVA patients' activities of daily living.

32 Barreiro TJ, Perillo I. An Approach to Interpreting Spirometry. Am Fam Physician 2004;69:1107-14

6.1.7 Subpopulations

The efficacy results of the 6MWT and 3MSC were different by baseline 6MWT category and age. The efficacy results stratified by the baseline 6MWT category have been discussed in Sections 6.1.4. and 6.1.5, and therefore, will not be discussed in this section.

An analysis on the change in 6MWD by age group found that the 12-18 years group performed best. Patients of this age subgroup in the QOW treatment group had a mean 6MWD increase of 24 (CI95 -12, 60) meters when compared to placebo, while the 5-11 age group decreased by 12 (CI95 -37, 14) meters and the ≥ 19 years age group increased by 3 (CI95 -37, 41) meters. Patients of the 12-18 year old subgroup in the QW treatment group had a mean 6MWD change of 48 (CI95 12, 84) meters when compared to placebo, while the 5-11 and ≥ 19 year old age groups increased by 14 (CI95 -12, 39) meters and 10 (CI95 -30, 52) meters, respectively.

The change in 3MSC by age did not find a consistent pattern. In the QOW treatment group, patients aged ≥ 19 years performed the best when compared to placebo, with an increase of 6 stairs/min (CI95 -1, 13). However, in the QW treatment group, patients aged 12-18 years performed the best when compared to placebo, with an increase of 3 stairs/min (CI95 -3, 10).

Medical Officer's Comment
The performance on the 6MWT by the age 12-18 years subgroup again speaks to elosulfase alfa demonstrating greater improvement in the patients who walked ≤ 200 meters at baseline.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In Trial MOR004, two dosing regimens were evaluated: elosulfase alfa 2 mg/kg weekly (QW) and elosulfase alfa 2 mg/kg every other week (QOW). The QW treatment group demonstrated a statistically significant change from baseline on the primary endpoint, 6MWT; however, this group did not show a statistically significant change from placebo on the secondary endpoint, 3MSC. The QOW treatment group was no different from placebo in either the 6MWT or the 3MSC. BioMarin has proposed the QW dosing regimen for the product labeling.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy is a concern for any drug that will be administered chronically. The data from long-term studies (MOR005 and MOR100) have not shown continued improvement in the 6MWT performance. For Trial MOR005, the 48-week data is difficult to interpret since only half of the QW-QW treatment group participated in that visit (n=26). Results from patients who received elosulfase alfa QW for 72 weeks

demonstrated no additional improvement on the 6MWT than the initial 22.5 meters gained at week 24 of treatment. A sensitivity analysis of 6MWT performance from those 26 patients who were assessed at week 48 and week 72 of treatment reveals no difference in mean change from baseline at these two timepoints.

There are various challenges to long term assessment of treatment benefit in the MPS IVA population. Long-term data are influenced by the frequent occurrence of orthopedic surgeries and the potential censoring of post surgical data. This makes long term assessment difficult in the open-label Trial MOR005 where orthopedic surgeries are allowed. See Figure 14 below. In addition, there may be an immunologic influence on the efficacy response because most patients develop persistent anti-drug antibodies, both binding and neutralizing types. The anti-drug antibodies appear to affect the uptake of the enzyme into the cell and could have contributed to suboptimal results of the efficacy endpoints, as well as less impressive pharmacodynamic results. (See Section 7.4.6 Immunogenicity.) It is not clear that a better assessment of long term efficacy is possible in patients who require frequent orthopedic surgeries. There is, however, potential to demonstrate greater clinical benefit. This may be evaluated in a placebo-controlled clinical trial with a higher dose of elosulfase alfa and/or a tolerance induction protocol to decrease the anti-drug antibody effect.

6.1.10 Additional Efficacy Issues/Analyses

On October 28, 2013, BioMarin shared with the Agency the additional analyses requested by the European Medicines Agency during this review cycle. Relevant clinical information is summarized in this section.

Additional Data from the Prospective Longitudinal Natural History Study (MOR001)
BioMarin reports that patients who have been enrolled in MOR001 have completed annual assessments and demonstrate the progressive deterioration of 6MWT performance over time. The annualized estimate of change in 6MWT from Visit 1 across all subjects in MOR001 was -5.2 meters (CI95, -11.5, 1.1). The annualized estimate of change in 6MWT from Visit 1 was -7.1 meters (CI95, -17.6, 3.3) in the subset of patients selected to match the MOR-004 study population (age ≥ 5 years, 6WMT between 30 and 325 meters at Visit 1). BioMarin asserts that the 6MWT is capable of measuring this decline in performance, but the lack of similar decline in the placebo treatment group of MOR004 speaks to a sizeable placebo effect. They further postulate that the performance of the placebo group in MOR004 “under-represents the true benefit of treatment”.

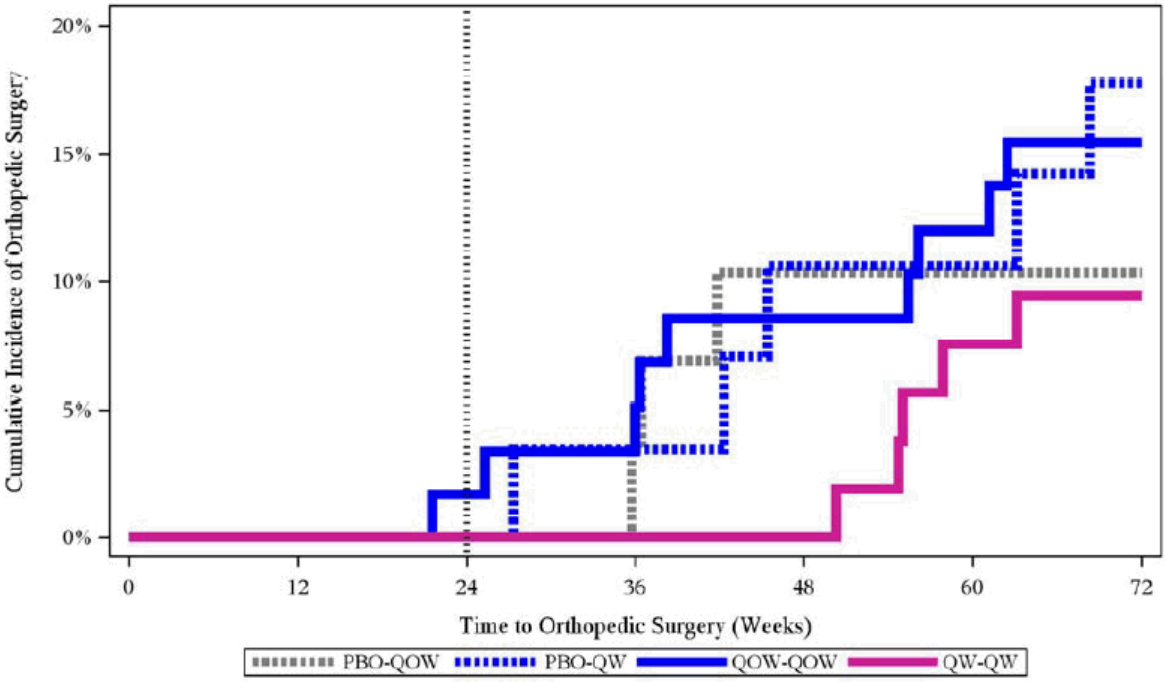
Medical Officer Comment
Although it is helpful to understand the rate of decline on the 6MWT in MPS IVA patients, this reviewer disagrees that the lack of decline in 6MWT performance in the placebo treatment group of MOR004 under-represents a true treatment

benefit. The advantage of a randomized, controlled trial is to be able to discern true drug benefit from placebo effect. The result of the primary endpoint of MOR004 stands on its own and should not be considered to be more than demonstrated.

Time to Orthopedic Surgery

BioMarin presented analyses on time to orthopedic surgery in Trials MOR004 and MOR005. It appears that fewer surgeries were performed in patients who have continuously received elosulfase alfa 2 mg/kg QW. In addition, patients in the QOW and placebo groups had surgeries earlier in the course of MOR-005 than those in the QW treatment group. BioMarin finds that these data suggest elosulfase alfa treatment reduces or delays the need for orthopedic surgery, but commits to evaluating time to orthopedic surgery and other long term clinical outcomes (e.g., wheelchair/walking aid dependence, mechanical ventilation, hospitalizations, hearing loss, visual acuity, bone marrow/stem cell transplant, growth, ECG/ECHO, skeletal surveys, and assessments of pain and quality of life) in a 10-year patient registry.

Figure 14: Time to Orthopedic Surgery in MOR004 and MOR005



From Figure 103.7, BioMarin's Response to October 18, 2013 FDA Request.

Medical Officer Comment

This reviewer is encouraged by the relatively delayed time to orthopedic surgery in the QW treatment group when compared to the other treatment groups. Because orthopedic surgery was a protocol violation in Trial MOR004, it is

important to see the comparison between treatment groups during Trial MOR005. It is curious, however, that the incidence of orthopedic surgery increases at a similar rate amongst all treatment groups. Long term data beyond 72 weeks would be helpful to support the reduction in rate of orthopedic surgery as a benefit of elosulfase alfa treatment.

7 Review of Safety

Safety Summary

The safety population is comprised of all 235 patients enrolled in the six elosulfase alfa clinical trials. The majority of patients (95%, 222 of 235) were treated with elosulfase alfa 2.0 mg/kg QW (the proposed marketing dosing regimen) for a duration from one week to 100 weeks. Fifty of these patients were treated with elosulfase alfa 2.0 mg/kg QW for ≥ 52 - 102 weeks. Among the 235 patients, the overall mean (± SD) duration of exposure was 50.2 (± 37) weeks.

There was a ninety six percent (226 of 235 patients) incidence of adverse events (AE) in patients receiving at least 1 dose of elosulfase alfa. The majority (75%, 175 of 235) of patients experienced drug-related AEs. The incidence of drug-related AEs decreased by approximately 20% once patients were beyond the first 12 weeks of treatment; however, incidence appears to stabilize between weeks 13 and 48. The most common adverse reactions occurring in ≥10% of the total safety population were pyrexia (26%), vomiting (22%), headache (20%), nausea (18%), abdominal pain (14%) and fatigue (12%). In MOR-004, the most common adverse reactions occurring in ≥10% of patients treated with elosulfase alfa and with a higher incidence than in the placebo-treated patients were pyrexia (33%), vomiting (31%), headache (26%), nausea (24%), abdominal pain (21%), chills (10%) and fatigue (10%).

There were no deaths. Twenty-nine percent of patients had serious AEs (SAEs), of which 10.6% were considered drug-related. Most SAEs were related to the underlying MPS IVA disease or infusion site conditions. The most commonly reported SAEs were knee deformity (7%) and poor venous access (3%), otitis media (2%), and lower respiratory tract infection (2%). Those drug-related SAEs were commonly events of anaphylaxis, severe hypersensitivity, or reactions that occurred during infusion. Eighteen patients were determined to have had anaphylaxis, seven patients experienced serious hypersensitivity reactions and 20 patients had reactions during infusion which were SAEs. Two patients discontinued due to severe hypersensitivity reactions.

The significant AEs for elosulfase alfa and all ERTs are anaphylaxis and hypersensitivity reactions. The incidence of anaphylaxis amongst MPS IVA patients treated with elosulfase alfa is 7.7%. This indicates 26 anaphylaxis events in 18

patients. Signs and symptoms in these reported cases have included dyspnea, bronchospasm, cough, hypoxia, hypotension, flushing, angioedema of the throat, urticaria, and gastrointestinal symptoms (e.g., nausea, abdominal pain, retching, and vomiting) in conjunction with urticaria. Anaphylaxis occurred as early as 30 minutes from the time of infusion but as late as 3.25 hours after infusion. Anaphylaxis has occurred as late into treatment as the 47th infusion.

Hypersensitivity reactions were reported for 64 (27%) patients. Recurrent hypersensitivity reactions were frequently demonstrated in those who experienced hypersensitivity. The most commonly reported hypersensitivity reactions were angioedema with a 25% incidence, urticaria (9%), "hypersensitivity" (5%), peripheral edema (5%), wheezing (4%), flushing (2%), cough (2%) and nasal obstruction (2%).

All patients treated with elosulfase alfa once per week developed anti-drug antibodies by Week 4. Anti-drug antibody titer levels were sustained in all patients over the course of treatment. Approximately 96% of patients who received elosulfase alfa once per week were positive for neutralizing antibodies at Week 16.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety population is comprised of all 235 patients enrolled in the six elosulfase alfa clinical trials as previously described in 5.1 Tables of Studies/Clinical Trials of this document. The six trials include the completed pivotal double-blind, placebo-controlled Phase 3 trial (MOR-004) and its ongoing extension trial (MOR-005), the completed Phase 1/2 trial (MOR-002) and its ongoing extension trial (MOR-100), and two ongoing ancillary Phase 2 trials (MOR-007 and MOR-008). Data from these clinical trials have been integrated for the review of safety.

7.1.2 Categorization of Adverse Events

Safety was assessed by examining the incidence, severity (categorized as mild, moderate, or severe), and relationship to study drug for all AEs that first occurred or worsened after initiation of the study drug (elosulfase alfa or placebo), whether or not the AE had a causal relationship to study treatment. All AEs were coded and summarized by system organ category (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0. AEs termed "infusion reactions" were defined as reactions occurring after initiation of infusion until the end of the day following the infusion. Those AEs identified as hypersensitivity reactions

resulted from a search of the safety database for AEs that matched the broad Angioedema Standardized MedDRA Query (SMQ) and/or the broad Anaphylactic Reaction algorithmic SMQ.

Medical Officer's Comments
In this review, adverse reactions identified as infusion reactions will be considered as drug-related adverse reactions.
It is noted that splitting of AE terms occurred for rash and abdominal pain. This reviewer has combined terms to re-calculate the incidences of these AEs. For example, the incidence of "abdominal pain" and "upper abdominal pain" were combined for a single incidence of abdominal pain.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The analyses for the integrated summary of safety are presented for the safety population of all patients exposed to elosulfase alfa in the six clinical trials. This includes all patients who received at least 1 dose (or any portion of a dose) of elosulfase alfa at doses of 0.1, 1.0, 2.0, or 4.0 mg/kg/week or 2.0 mg/kg every other week for periods ranging from 1 week to 170 weeks. The majority of patients (95%, 222 of 235) were treated with elosulfase alfa 2.0 mg/kg QW (the proposed marketing dosing regimen) for 1 week to 100 weeks. Fifty of these patients were treated with elosulfase alfa 2.0 mg/kg QW for ≥ 52 - 102 weeks. Among the 235 patients, the overall mean (± SD) duration of exposure was 50.2 (± 37) weeks. The mean (± SD) weekly elosulfase alfa dose per patient was 1.64 (± 0.69) mg/kg. The mean (± SD) total elosulfase alfa dose per patient was 73.2 (± 54.37) mg/kg. Table 23 further details elosulfase alfa exposure by dose in each clinical trial.

Table 23: Drug Exposure by Clinical Trials and Treatment Regimen

	MOR-004 2.0 mg/kg		MOR-005 2.0 mg/kg				MOR-002 <= 2.0 mg/kg	MOR-100 2.0 mg/kg	MOR-007 2.0 mg/kg	MOR-008		
	QOW (n=59)	QW (n=58)	PBO-QOW (n=29)	PBO-QW (n=29)	QOW-QOW (n=59)	QW-QW (n=56)	QW (n=20)	QW (n=17)	QW (n=15	2.0 mg/kg/QW (n=15)	4.0 mg/kg/QW (n=10)	Total (n=235)
Total Study Drug Exposure (weeks)												
n	59	58	29	29	59	56	20	17	15	15	1	235
Mean (SD)	24.0 (0.19)	23.6 (3.03)	32.9 (13.17)	31.7 (14.27)	31.6 (13.53	32.4 (14.95)	69.5 (22.05)	82.9 (3.46)	24.8 (9.12	11.6 (4.59	10.0 (3.5	50.2 (37.03)
Median	24.0	24.0	29.1	29.0	24.0	26.0	78.4	84.0	26.9	10.3	9.	44.6
Min, Max	23.3, 24.4	1.0, 25.0	19.9, 66.0	11.0, 75.6	11.0, 76.6	1.0, 76.1	9.1, 84.0	74.0, 87.0	8.0, 44.0	6.4, 20.0	6.4, 15.9	1.0, 169.7
Mean Weekly Dose/Patient (mg/kg)												
n	59	58	29	29	59	56	20	17	15	15	1	235
Mean (SD)	0.99 (0.03)	1.96 (0.07)	1.99 (0.02)	2.00 (0.004)	1.99 (0.03)	1.99 (0.03)	0.91 (0.28)	1.99 (0.07)	1.91 (0.146	1.95 (0.08	3.96 (0.17	1.64 (0.69)
Median	1.00	1.99	2.00	2.00	2.00	2.00	1.00	2.00	1.96	1.99	4.0	1.90
Min, Max	0.88, 1.03	1.68, 2.05	1.93, 2.00	1.98, 2.01	1.75, 2.01	1.83, 2.01	0.09, 1.06	1.87, 2.20	1.50, 2.04	1.73, 2.04	3.72, 4.22	0.09, 4.22
Total Dose/Patient (mg/kg)												
n	59	58	29	29	59	56	20	17	15	15	10	235
Mean (SD)	23.7 (0.70)	46.2 (6.18)	62.2 (25.11)	60.9 (27.60)	60.2 (25.94)	61.0 (27.66)	65.6 (23.74)	147.3 (22.09)	48.0 (18.88)	22.8 (9.29)	39.7 (14.64)	73.2 (54.37)
Median	24.0	48.0	51.9	54.1	44.0	49.1	72.0	152.1	49.9	20.1	36.5	55.0
Min, Max	21.0, 24.3	1.8, 48.1	36.0,	20.0,	20.0,	2.0, 136.0	0.8, 83.9	91.7, 171.4	12.0, 88.1	12.0, 40.1	23.9, 64.4	0.8, 251.7

* BioMarin's Table 2.7.4.1.2.1, Summary of Clinical Safety 2.7.4, p.5.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A closer look at the study population by duration of exposure demonstrates that the number of patients exposed to elosulfase alfa decreases with each increasing 12-week time interval. The mean weekly elosulfase alfa dose per patient was similar across each time interval. As expected, the mean total elosulfase alfa dose per patient increased with longer time on treatment. Table 24: Duration of Drug Exposure in Safety Population displays the duration of elosulfase alfa exposure by each 12-week interval between 1 to 48 weeks, as well as a > 48-week interval.

Table 24: Duration of Drug Exposure in Safety Population

	Duration of Dosing Weeks					
	1-12 (n=235)	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
Total Study Drug Exposure (weeks)						
Mean (SD)	50.2 (37.03)	55.0 (36.13)	62.4 (35.68)	67.4 (35.87)	84.4 (39.68)	50.2 (37.03)
Median	44.6	45.3	48.1	52.5	67.1	44.6
Min, Max	1.0, 169.7	15.0, 169.7	25.0, 169.7	37.6, 169.7	49.0, 169.7	1.0, 169.7
Mean Weekly Dose/Patient (mg/kg)						
Mean (SD)	1.64 (0.686)	1.55 (0.534)	1.51 (0.474)	1.48 (0.471)	1.50 (0.449)	1.64 (0.686)
Median	1.90	1.64	1.52	1.50	1.51	1.90
Min, Max	0.09, 4.22	0.94, 4.06	0.94, 2.02	0.94, 2.00	0.96, 2.00	0.09, 4.22
Total Dose/Patient (mg/kg)						
Mean (SD)	73.2 (54.37)	79.2 (54.05)	88.9 (54.59)	95.4 (55.87)	119.1 (61.57)	73.2 (54.37)
Median	55.0	63.0	72.3	84.4	104.0	55.0
Min, Max	0.8, 251.7	18.0, 251.7	25.0, 251.7	37.1, 251.7	42.8, 251.7	0.8, 251.7

* BioMarin's Table 2.7.4.1.2.2, Summary of Clinical Safety 2.7.4, p.7.

Across all treatment duration intervals, the ages of patients at enrollment ranged from 0.8 to 57.4 years. The majority of patients across all treatment duration intervals were under 12 years old, White, and not Hispanic or Latino. Males and females were distributed evenly across treatment duration intervals. Seventy four (31.5%) patients were enrolled at North American trial centers; 106 (45.1%), at European centers; and 55 (23.4%), at centers in other regions. Table 25 further describes the demographics of the safety population.

Table 25: Demographics of the Clinical Safety Population

		Duration of Dosing, Weeks					
		1-12 (n=235)	13-24 (n=211)	25-36 (n=174)	37-48 (n=150)	>48 (n=86)	Total (n=235)
Age at Enrollment, years	n	235	211	174	150	86	235
	Mean (SD)	13.2 (9.67)	13.1 (9.86)	13.1 (9.89)	13.4 (10.07)	13.0 (10.20)	13.2 (9.67)
	Median	10.5	10.0	10.3	10.3	9.7	10.5
	Min, Max	0.8, 57.4	0.8, 57.4	1.4, 57.4	2.1, 57.4	4.9, 57.4	0.8, 57.4
Age Group (years)	0 to <5	16 (6.8%)	14 (6.6%)	10 (5.7%)	2 (1.3%)	1 (1.2%)	16 (6.8%)
	5 to <12	124 (52.8%)	114 (54.0%)	95 (54.6%)	89 (59.3%)	53 (61.6%)	124 (52.8%)
	12 to <19	56 (23.8%)	47 (22.3%)	42 (24.1%)	36 (24.0%)	19 (22.1%)	56 (23.8%)
	>=19	39 (16.6%)	36 (17.1%)	27 (15.5%)	23 (15.3%)	13 (15.1%)	39 (16.6%)
Sex	Female	121 (51.5%)	104 (49.3%)	84 (48.3%)	70 (46.7%)	43 (50.0%)	121 (51.5%)
	Male	114 (48.5%)	107 (50.7%)	90 (51.7%)	80 (53.3%)	43 (50.0%)	114 (48.5%)
Race	Asian	53 (22.6%)	53 (25.1%)	49 (28.2%)	41 (27.3%)	23 (26.7%)	53 (22.6%)
	Black or African American	4 (1.7%)	4 (1.9%)	4 (2.3%)	4 (2.7%)	2 (2.3%)	4 (1.7%)
	White	156 (66.4%)	137 (64.9%)	106 (60.9%)	92 (61.3%)	57 (66.3%)	156 (66.4%)
	Other	22 (9.4%)	17 (8.1%)	15 (8.6%)	13 (8.7%)	4 (4.7%)	22 (9.4%)
Ethnicity	Hispanic or Latino	44 (18.7%)	40 (19.0%)	29 (16.7%)	27 (18.0%)	6 (7.0%)	44 (18.7%)
	Not Hispanic or Latino	191 (81.3%)	171 (81.0%)	145 (83.3%)	123 (82.0%)	80 (93.0%)	191 (81.3%)
Region	North America	74 (31.5%)	57 (27.0%)	44 (25.3%)	36 (24.0%)	24 (27.9%)	74 (31.5%)
	Europe	106 (45.1%)	99 (46.9%)	85 (48.9%)	72 (48.0%)	54 (62.8%)	106 (45.1%)
	Other	55 (23.4%)	55 (26.1%)	45 (25.9%)	42 (28.0%)	8 (9.3%)	55 (23.4%)

* BioMarin's Table 2.7.4.1.3.1.1, Summary of Clinical Safety 2.7.4, p. 10.

The medical history of the safety population was similar to that understood in the medical literature. Patients commonly reported musculoskeletal and connective tissue disorders, including corneal opacity, knee deformity, kyphosis and pectus carinatum. Although varied by individual clinical trial, a high proportion (60-85%) of patients in the safety population reported surgical and medical procedures.

7.2.2 Explorations for Dose Response

Based on preliminary evidence of improvement in efficacy measures in the Phase 1/2 Trials MOR002 and MOR100, BioMarin determined that the elosulfase alfa 2.0 mg/kg weekly dose would be pursued for marketing dose. BioMarin, however, explored two dosing regimens in the pivotal Trial MOR004: once per week (QW) and once every other week (QOW) dosing of elosulfase alfa 2.0 mg/kg. The comparison of these dosing regimens demonstrates no clear difference in incidence of AEs. The AE incidence by elosulfase alfa dosing regimen is discussed below in Section 7.3 Major Safety Results.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

The assessment of patient safety was conducted by monitoring for adverse events, concomitant medication use, and surgical procedures, vital signs, physical examinations, clinical laboratory testing (clinical chemistry, hematology, and urinalysis), 12-lead ECGs, ECHO, and monitoring of anti-idursulfase antibodies.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal studies of drug-drug interaction have been performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Risk of severe hypersensitivity reactions and the development of antibodies against therapeutic proteins are adverse reactions known to all enzyme replacement therapies (ERT). These safety risks are discussed below in Sections 7.3 Major Safety Results and 7.4.6 Immunogenicity. Further information on these risks with ERTs are presented above in Section 2.5 Important Safety Issues With Consideration to Related Drugs.

7.3 Major Safety Results

There was a 96% (226 of 235 patients) incidence of AEs in patients receiving at least 1 dose of elosulfase alfa. The majority (75%, n=175) of these patients experienced drug-related AEs, and 10.6% experienced serious AEs (SAEs). In patients exposed to elosulfase alfa 2 mg/kg QW, the incidence rates were slightly lower with 77% (171 of 222) experiencing AE. Approximately half (52%) experienced drug-related AE, with 7.2% considered SAEs. There were no deaths in any of the clinical trials; however, two patients discontinued due to anaphylaxis and severe hypersensitivity reaction. Table 26 displays the distribution of AEs in all patients in the safety population, as well as those who received the weekly dosing regimen of elosulfase alfa 2 mg/kg QW.

Table 26: Summary of Adverse Events in the Safety Population

	Incidence: n (%)
All Exposed Patients	**Total (n=235)**
AE	226 (96.2%)
Drug-Related AE	175 (74.5%)
SAEs	69 (29.4%)
Related SAEs	25 (10.6%)†
AE leading to discontinuation	2 (0.8%)
Patients on elosulfase alfa 2.0 mg/kg QW	**Total (n=222)**
AE	171 (77.0%)
Drug-Related AE	116 (52.3%)
SAEs	39 (17.6%)
Related SAEs	16 (7.2%)†
AE leading to discontinuation	0

Modified from BioMarin's Table 2.7.4.2.1.2 and Table 2.7.4.2.1.3, Summary of Clinical Safety 2.7.4, p. 18-19.
† Incidence of drug-related SAEs recalculated by FDA reviewer to include additional identified cases of anaphylaxis.

In Trial MOR004, the majority of patients in each treatment group reported an AE. There were 57 (97%) patients in the placebo group, 59 (100%) patients in the QOW group and 56 (96.6%) patients in the QW group with at least one AE. Most AEs were considered drug-related AEs and were reported in 36 (61.0%) patients in the placebo group, 42 (71.2%) patients in the QOW group, and 42 (72.4%) patients in the QW group. Drug-related SAEs occurred in 4 (6.7%) of patients in the QOW group, and 9 (15.5%) of patients in the QW group. Table 27 summarizes the adverse events by treatment group in Trial MOR004.

Table 27: Summary of Adverse Events by Treatment Group (MOR004)

Incidence: n (%)	Placebo (n=59)	elosulfase alfa 2.0 mg/kg QOW (n=59)	elosulfase alfa 2.0 mg/kg QW (n=58)
AE	57 (96.6%)	59 (100.0%)	56 (96.6%)
Drug-Related AE	36 (61.0%)	42 (71.2%)	42 (72.4%)
SAE	2 (3.4%)	7 (11.8%)†	18 (31%)†
Drug-Related SAE	0 (0.0%)	4 (6.7%)†	9 (15.5%)†
AE Leading to Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Adapted from BioMarin Table 11.2.1.1, CSR MOR004, p.213.
† Twelve additional patients with anaphylaxis have been included by the FDA reviewer.

7.3.1 Deaths

There were no deaths due to the elosulfase alfa reported in the clinical trials.

7.3.2 Nonfatal Serious Adverse Events

MPS IVA patients participating in the six clinical trials often experienced serious adverse events (SAE) related to their underlying disease or infusion site conditions. SAEs were experienced by 69 (29%) patients enrolled in clinical trials: 49 patients had single SAEs and the other 20 patients had > 1 SAE. The most commonly reported SAEs were knee deformity (7%), poor venous access (3%), otitis media (2%), and lower respiratory tract infection (2%). Other SAEs occurred in 1% (n=3) or fewer patients. Patients with repeated SAEs include Patient MOR002-0121-2003 who had five SAEs during infusions

on different days and Patient MOR002-0121-2012 who had three episodes of flushing or infusion site reactions on three different days.

The drug-related SAEs were commonly events of anaphylaxis, severe hypersensitivity, or reactions that occurred during infusion. Twenty patients had reactions during infusion, seven patients experienced hypersensitivity reactions, and eighteen patients had anaphylaxis events that were considered SAEs. One patient in the Phase 1/2 trial MOR002 was the first to experience anaphylaxis in the clinical development program. This event occurred during the patient's 10^{th} infusion, after which the patient discontinued from the trial. All clinical trial protocols were then amended to require that patients receiving elosulfase alfa are pre-medicated with non-sedating antihistamine. The narrative of the first patient who experienced anaphylaxis is described below:

- **Patient MOR002-0119-2007**
  Patient 0119-2007 experienced a Type 1 hypersensitivity reaction on Week 11 during the tenth infusion of elosulfase alfa 0.1 mg/kg QW. The patient had not been pre-treated with an antihistamine or an antipyretic. The infusion was initiated at a rate of 1.4 mL/hr in accordance with the protocol. The rate was increased to 18.5 mL/hr after 1 hour. Five minutes after the rate increase, the patient experienced symptoms of generalized urticaria, edema, and difficulty breathing with stridor and wheezing. The infusion was immediately discontinued and the patient was treated with oxygen, hydrocortisone, adrenaline, and chlorpheniramine maleate. Tryptase and complement levels obtained at the time of the reaction were normal, and O_2 saturation was 100%. Total IgE was elevated and a positive drug-specific IgE was obtained at the time of the reaction. The event resolved 1 day after onset. The patient discontinued from the trial after Week 11.

Narratives for patients who experienced drug-related SAEs of hypersensitivity and anaphylaxis are provided in the Appendix of this document.

In Trial MOR004, more SAEs were demonstrated in the elosulfase alfa treatment groups when compared to placebo. The most common SAEs, however, were related to the underlying disease or anaphylaxis. See Table 28 below for details.

Table 28: Serious Adverse Events in Trial MOR004

Preferred Term	Placebo (n = 59)	elosulfase alfa 2.0 mg/kg QOW (n = 59)	elosulfase alfa 2.0 mg/kg QW (n = 58)
Patients with at Least 1 Reported SAE	2 (3.4%)	7 (11.8%)†	18 (31%)†
Pneumonia	0	0	2 (3.4%)
Hypersensitivity	0	0	1 (1.7%)
Infusion site pain	0	0	1 (1.7%)
Lower respiratory tract infection	0	0	1 (1.7%)
Otitis media	0	1 (1.7%)	1 (1.7%)
Urticaria	0	0	1 (1.7%)
Viral upper respiratory tract infection	0	0	1 (1.7%)
Vomiting	0	0	1 (1.7%)
Anaphylactic reaction†	0	4(6.7%)†	9 (15.5%)†
Cervical cord compression	1 (1.7%)	0	0
Deafness	1 (1.7%)	0	0
Dengue fever	0	1 (1.7%)	0
Suture removal	0	1 (1.7%)	0

*BioMarin's Table 2.7.4.2.2.2.1, CSS, p. 33.
† Twelve additional patients with anaphylaxis have been included by the FDA reviewer.

The SAEs determined to be drug-related included thirteen patients with anaphylactic reactions. These patient narratives are presented in the Appendix, and anaphylaxis is further discussed in Section 7.3.4.

7.3.3 Dropouts and/or Discontinuations

As described above, two patients discontinued due severe hypersensitivity reactions. Patient MOR-002-0119-2007 experienced an AE during the 1 to 12-week interval that resulted in permanent trial discontinuation. Patient MOR002-0121-2003 experienced recurrent reactions primarily characterized by skin (urticaria) and gastrointestinal (abdominal pain, vomiting) symptoms. The patient discontinued treatment after week 45, but remained enrolled in the trial. Additional details on patient MOR002-0121-2003 are provided in the Appendix.

7.3.4 Significant Adverse Events

The significant AEs for elosulfase alfa and all ERTs are anaphylaxis and hypersensitivity reactions. Hypersensitivity reactions were reported in 64 (27%) patients. The most commonly reported hypersensitivity reactions were angioedema with a 25% incidence, urticaria (9%), "hypersensitivity" (5%), peripheral edema (5%), wheezing (4%), flushing (2%), cough (2%) and nasal obstruction (2%). All other hypersensitivity reactions occurred in 1% (n=3) or fewer patients.

In Trial MOR004, more hypersensitivity reactions occurred in the elosulfase alfa treatment groups (QOW: 27%, QW: 21%) when compared to placebo (12%). In the elosulfase alfa treatment groups, the events of flushing, dyspnea, urticaria, "hypersensitivity", and peripheral edema occurred in more than one patient and at a greater frequency than placebo. Table 29 below shows the incidence of hypersensitivity in Trial MOR004.

Table 29: Hypersensitivity Reactions in Trial MOR004

	Placebo (n=59) Incidence	elosulfase alfa 2.0 mg/kg/qow (n=59) Incidence	elosulfase alfa 2.0 mg/kg/week (n=58) Incidence
Patients with a Least 1 Hypersensitivity AE	7 (11.9%)	16 (27.1%)	12 (20.7%)
Anaphylactic Reaction SMQ	1 (1.7%)	2 (3.4%)	3 (5.2%)
Flushing	0	1 (1.7%)	2 (3.4%)
Cough	1 (1.7%)	0	1 (1.7%)
Dyspnea	0	1 (1.7%)	1 (1.7%)
Hypotension	0	0	1 (1.7%)
Urticaria	0	0	1 (1.7%)
Anaphylactic reaction	0	1 (1.7%)	0
Lip swelling	1 (1.7%)	0	0
Angioedema SMQ	7 (11.9%)	14 (23.7%)	10 (17.2%)
Urticaria	0	4 (6.8%)	4 (6.9%)
Hypersensitivity	1 (1.7%)	4 (6.8%)	3 (5.2%)
Eyelid edema	0	0	1 (1.7%)
Obstructive airways disorder	0	0	1 (1.7%)
Edema peripheral	2 (3.4%)	4 (6.8%)	1 (1.7%)
Throat tightness	0	0	1 (1.7%)
Wheezing	1 (1.7%)	0	1 (1.7%)
Auricular swelling	1 (1.7%)	0	0
Lip swelling	1 (1.7%)	1 (1.7%)	0
Nasal obstruction	2 (3.4%)	1 (1.7%)	0
Edema	1 (1.7%)	0	0
Stridor	0	1 (1.7%)	0

*BioMarin's Table 2.7.4.2.3.2.1, CSS, p. 46.

Most hypersensitivity reactions were mild or moderate, although severe hypersensitivity was experienced by seven patients. The narratives for patients MOR002-0119-2007, MOR002-0121-2003, MOR004-1075-4007, MOR004-0020-4141, and MOR004-0021-4005 were previously described above under drug-related SAEs. The additional patient narratives are listed here.

- **Patient 0109-4025**

Patient 0109-4025 is a 5-year-old female who experienced a severe, non-serious event of chills. She received her first infusion of elosulfase alfa 2.0 mg/kg/week on 17

August 2011. The last dose prior to event onset was administered on 2 November 2011. The patient had a series of non-serious infusion-related reactions requiring medical intervention, starting with dose 3 on 7 September 2011 (urticaria and upper abdominal pain treated with IV antihistamines). She developed fever and nausea requiring ibuprofen and fluids during dose 9 on 19 October 2011. Prior to both of those infusions, premedications included diphenhydramine but did not include corticosteroids or antipyretics. During both of these doses, the infusions were interrupted as a result of the events, but later restarted and completed. On 2 November 2011, the infusion (dose 11) was started at about 8:45 a.m. after premedication with diphenhydramine. At about 9:35 a.m., the patient developed non-serious, severe chills, along with non-serious mild-to-moderate headache, upper abdominal pain, throat irritation, and oropharyngeal pain. Treatment for the events included IV diphenhydramine and IV prednisolone. The infusion was interrupted, then resumed after a several hour break at a lower infusion rate and ultimately completed. The event of chills was considered resolved later that day. Starting with the next infusion, additional premedication with steroids and anti-pyretics was added for each infusion day. The patient had an infusion interruption as a result of non-serious adverse events with the next infusion on 11 November 2011, but not again after that through the end of the trial. The Investigator assessed the event of chills as probably related to study treatment.

- **Patient MOR004-1075-4007**

Patient 1075-4007 is a 6-year-old male (age at time of enrollment in MOR-004) who experienced a non-serious grade 3 anaphylactic reaction. He started treatment in MOR-004 with elosulfase alfa 2.0 mg/kg/qow on (b) (4) and he received his first dose in MOR-005 on 30NOV2011. On 04MAY2012, his pre-infusion vital signs included temperature 36.6°C, BP 98/53, pulse 93, and respiratory rate 22. Pre-medication with anti-histamine was given, and the infusion was started. Approximately one hour into the infusion, the patient developed a non-serious grade 3 anaphylactic reaction. His vital signs at the time included BP 81/33. The infusion was temporarily discontinued, and treatment with IV antihistamines and IV steroids was given. The patient's blood pressure had risen to 121/77 approximately 15 minutes after the onset of the anaphylactic reaction. Approximately 2 hours after the reaction started, it was considered to have resolved; the infusion was restarted at a lower infusion rate and was completed. The patient received his next dose of study treatment on 11MAY2012, and he remained on the trial. The investigator assessed the event of anaphylactic reaction as probably related to study treatment.

BioMarin identified three patients with anaphylaxis (Patient MOR002-0119-2007, Patient MOR004-0021-4005, and Patient MOR004-1075-4007).

Medical Officer's Comment

Because this reviewer noted several additional patients who met the NIAID/FAAN criteria, an information request for additional query of the safety database for cases of anaphylaxis as defined by the NIAID/FAAN criteria was issued. The

***NIAID/FAAN criteria for anaphylaxis do not require the presence of IgE antibody to define this life-threatening event. These criteria are shown in* Figure 15.**

Figure 15: National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Criteria for Anaphylaxis (2006) †

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pru
   flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 and less than 90 mm Hg from 11 to 17 years.

† Sampson H et al. J Allergy Clin Immunol 2006;117:391-7

BioMarin subsequently provided a listing of sixteen patients who met the criteria for anaphylaxis. The narratives of these patients, as well as all those patients who experienced hypersensitivity were re-adjudicated by this reviewer and Dr. T. Kruzick, Medical Officer from the Division of Pulmonary, Allergy, and Rheumatology Products. Two additional cases of anaphylaxis were identified to correspond with the NIAID/FAAN criteria 2006 #1. These two cases bring the final incidence of anaphylaxis to 7.7%. This indicates 18 patients with 26 anaphylaxis events. The patients identified to have experienced anaphylaxis are listed below.

Patients with anaphylaxis:

1. ***MOR002-0119-2007***
2. ***MOR002-0121-2003***
3. ***MOR004-0020-4141***
4. ***MOR004-0021-4005***
5. ***MOR004-0021-4103***
6. ***MOR004-0050-4063***
7. ***MOR004-0109-4025***
8. ***MOR004-0109-4028***
9. ***MOR004-0111-4019***
10. ***MOR004-0121-4139***
11. ***MOR004-1017-4016***
12. ***MOR004-1075-4007***
13. ***MOR004-1075-4050***
14. ***MOR004-1159-4109***
15. ***MOR004-1159-4117***
16. ***MOR004-1167-4068***
17. ***MOR007-0018-7005***
18. ***MOR008-0109-8106***

A brief description of the anaphylaxis events are listed in Table 33: Descriptions of Anaphylaxis Events ***in the Appendix of this document.***

The risk of anaphylaxis and severe hypersensitivity reactions are present with elosulfase alfa. With an anaphylaxis incidence of 8%, a boxed warning similar to that of other ERTs needs to be added to the product labeling.

Reactions Associated with Infusion

BioMarin defined any AE that occurred after the onset of the infusion and within 1 day following the end of the infusion as associated with the infusion. These reactions occurred in 93% (218 of 235) of the safety population, and the most commonly observed reactions associated with infusion were headache (37%), vomiting (36%) and pyrexia (35%). Patients were monitored closely during and after infusion for any AEs, and appropriate clinical management was instituted as needed. Clinical management included infusion interruption (i.e., the infusion was stopped and eventually completed at that visit), infusion discontinuation (i.e., that visit's infusion was never completed), medical intervention (defined as administration of intravenous steroids, intravenous antihistamines, intravenous fluids, or oxygen), or permanent study drug discontinuation. Infusion was interrupted in 40% of patients and discontinued in 17% of patients. Twenty-three percent of these reactions required medical intervention. The incidences of these reactions are further described below in Section 7.4.1 Common Adverse Events.

Medical Officer's Comments
The recent Agency position on the term (b) (4) is to eliminate the term from product labeling.[33] This recommendation is based on the fact that (b) (4) events may be interpreted differently by healthcare providers. Some of these events may be life-threatening anaphylaxis which requires emergent treatment. Therefore, the Agency now recommends categorizing events that occur during infusion as either 1) anaphylaxis 2) hypersensitivity reactions or 3) other. For the purpose of this review, reactions occurring during infusion that are not hypersensitivity reactions or anaphylaxis will be captured under the common AE discussion.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the 235 patients in the safety population, 226 (96%) experienced an AE. The most common SOCs were SOC of Gastrointestinal Disorders (79%), General Disorders And Administrative Site Conditions (76%), and Infections and Infestations (74%). The rate of Gastrointestinal Disorders was highest in the first 12 weeks of treatment.

Seventy-five percent (175 of 235) of patients experience drug-related AEs. The incidence of drug-related AEs decreased by approximately 20% once patients were beyond the first 12 weeks of treatment; however, incidence appears to stabilize between weeks 13 and 48. The most common drug-related AEs occurring in ≥10% of patients were pyrexia (26%), vomiting (22%), headache (20%), nausea (18%), abdominal pain (14%) and fatigue (12%). Except for the incidence of abdominal pain, which had to be calculated separately by the FDA clinical reviewer, Table 30 shows the incidence of these common drug-related AEs by 12-week time intervals of treatment.

33 Draft FDA Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, February 2013.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf

Table 30: Drug-Related Adverse Events with Incidence ≥10% in the Total Safety Population

Incidence: n (%)	Duration of Elosulfase Alfa Dosing, Weeks					
Preferred Term	**1-12 (n=235)**	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
Patients with at least 1 reported AE	142 (60.4%)	79 (37.4%)	58 (33.3%)	45 (30.0%)	36 (41.9%)	175 (74.5%)
Pyrexia	38 (16.2%)	15 (7.1%)	14 (8.0%)	6 (4.0%)	12 (14.0%)	61 (26.0%)
Vomiting	37 (15.7%)	16 (7.6%)	9 (5.2%)	8 (5.3%)	4 (4.7%)	51 (21.7%)
Headache	32 (13.6%)	18 (8.5%)	12 (6.9%)	10 (6.7%)	6 (7.0%)	48 (20.4%)
Nausea	31 (13.2%)	13 (6.2%)	10 (5.7%)	11 (7.3%)	1 (1.2%)	43 (18.3%)
Abdominal Pain[†]	n/a	n/a	n/a	n/a	n/a	33 (14%)
Fatigue	15 (6.4%)	5 (2.4%)	5 (2.9%)	3 (2.0%)	6 (7.0%)	27 (11.5%)

From BioMarin's Table 2.7.4.2.1.1.2, CSS, p. 27.
[†] Incidence of abdominal pain calculated by reviewer from data file.

For Trial MOR004, the most common SOCs were similar across all treatment groups. The most common SOCs were Infections and Infestations (66% placebo, 71% elosulfase alfa 2.0 mg/kg QOW, and 67% elosulfase alfa 2.0 mg/kg QW), General Disorders and Administration Site Conditions (63%, 68%, 66%), and Gastrointestinal Disorders (70%, 68%, 64%). The most common drug-related AEs were similar to that in the total safety population. Those occurring in ≥10% of patients and a higher frequency than placebo were pyrexia, vomiting, headache, nausea, abdominal pain, chills, and fatigue. The incidence of these AEs for the elosulfase alfa 2.0 mg/kg QW treatment group compared to the placebo group is shown in Table 31.

Table 31: Drug-Related Adverse Reactions Occurring in ≥10% of Patients and a Higher Frequency Than Placebo (Trial MOR004)

Adverse Reaction	Placebo N= 59 n(%)	elosulfase alfa QW N= 58 n(%)
Pyrexia	8 (14%)	19 (33%)
Vomiting	4 (7%)	18 (31%)
Headache	9 (15%)	15 (26%)
Nausea	4 (7%)	14 (24%)
Abdominal pain†	1 (1.7%)	12 (21%)
Chills	1 (1.7%)	6 (10.3%)
Fatigue	2 (3.4%)	6 (10.3%)

*Adapted from BioMarin's Table 14.3.1.3.3., CSR MOR004, p.2468.
† Incidence of abdominal pain calculated by reviewer from data file.

In the safety population, there were 35 (15%) patients who experienced severe AEs: 6 in Trial MOR004 and 30 in the other five clinical trials. Severe AEs related to elosulfase alfa occurred in eleven of the 35 patients and included the following:

Drug-related Severe AEs	Number of Patients
Anaphylaxis	2
Chills	1
Hypersensitivity	1
Hypertension	2
Infusion-related reaction	1
Pyrexia	2
Rash	1
Type I hypersensitivity	1
Upper respiratory tract infection	1
Vomiting	2

In Trial MOR004, the majority of AEs were of mild (52%) or moderate (42%) severity. Severe AEs were reported in 4% of patients, specifically with one patient in the placebo group, three patients in the elosulfase alfa 2.0 mg/kg QOW group, and two patients in the elosulfase alfa 2.0 mg/kg QW group. No severe AEs occurred more than once. A brief description of severe AEs are described here.

- In the placebo group
  - Patient MOR004-0111-4087 experienced cervical cord compression, which the investigator assessed as unrelated to treatment. Symptoms resolved without treatment the day after onset

- In the elosulfase alfa 2.0 mg/kg QOW group.
    - Patient MOR004-1075-4007, anaphylaxis (This patient also experienced a grade 3 AE of anaphylactic reaction while participating in MOR-005)
    - Patient MOR004-1017-4016, rash
    - Patient MOR004-0050-4070, joint dislocation
- In the elosulfase alfa 2.0 mg/kg QW group
    - Patient MOR004-0109-4025, chills
    - Patient MOR004-0020-4141, hypersensitivity

Medical Officer's Comment
Common drug-related AEs reflect the reactions known to occur during infusion of enzyme replacement therapies. The severe drug-related AEs exemplify the serious risks of anaphylaxis and severe hypersensitivity.

7.4.2 Laboratory Findings

Chemistry
Incidences of clinically significant serum chemistry results or changes from Baseline were uncommon, and elosulfase alfa treatment was not associated with a clinically meaningful increase in abnormalities of serum chemistry values.

In Trial MOR-004, few patients had post-Baseline out-of-range chemistry levels. The shifts from baseline normal to abnormal that were present occurred in similar frequencies across treatment groups, and no consistent or clinically meaningful changes from baseline in serum chemistry results were evident. In Trial MOR-005, Part 1, no treatment-related patterns, nor differences between cohorts over time, were apparent in changes from Baseline in chemistry at key study visits.

Liver Function Tests
Few treatment-emergent increases in liver function tests were apparent in patients treated with elosulfase alfa across all studies. A few liver enzyme increases were reported as AEs in each trial. These included two elosulfase alfa 2.0 mg/kg/ QW patients in Trial MOR-004 who had increased liver enzymes reported as AEs.

- Patient 1075-4050 had a moderate increase in liver transaminases at Study Day 140 (Week 20) that was considered possibly related to study drug and was ongoing; the last sample tested (Week 18) had a level < 2-fold higher than the upper limit of normal.
- Patient 1167-4066 had mild increases in alanine aminotransferase and gamma glutamyl-transferase that were considered not related to study drug (concurrent with pneumonia) and resolved within 2 weeks

Hematology
No evidence of treatment-emergent increases in hematology abnormalities was apparent in patients treated with elosulfase alfa across all studies. There were few reported hematology abnormalities in any treatment group, and incidences of clinically significant hematologic results and clinically significant changes from Baseline were uncommon. Elosulfase alfa treatment was not associated with a clinically meaningful increase in hematologic abnormalities.

In Trial MOR-004, the mean changes from Baseline for all hematology parameters were small and within normal ranges at all visits. All shifts in hematology were transient. No hematology test showed a clinically meaningful trend. In Trial MOR-005 Part 1, no treatment related patterns, nor differences between cohorts over time, were apparent in changes from Baseline in hematology.

Urinalysis
Across all studies, no evidence of treatment-emergent increases in urinalysis abnormalities was apparent in patients treated with elosulfase alfa. In MOR-004, no consistent or clinically meaningful changes from Baseline in urinalysis results were evident.

7.4.3 Vital Signs

Clinically significant abnormalities in vital signs were reported as AEs.

7.4.4 Electrocardiograms (ECGs)

In Trial MOR-004, ECGs were classified as one of the following categories: 1) normal, 2) abnormal, or 3) clinically significant abnormal. No study patient in any treatment group had a shift to a clinically significant abnormal ECG from Baseline to Week 24.

In Trial MOR-002, one patient (0121-2009) had an abnormal ECG at the Week 36 (1 of 19, 5.3%) and Week 72 (1 of 18, 5.6%) visits. This patient was noted to have an "Increased LV forces, no strain" at Screening, and "flattening of 'T' waves, especially lateral" at Weeks 36 and 72. The finding of 'flattening of 'T' waves' was also recorded as 'mild' AE, unrelated to study drug, commencing on study day 244, and unresolved at study completion.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

All patients treated with elosulfase alfa developed anti-drug antibodies. Total binding antibody (TAb) was sustained over the entire treatment period. Approximately 80% of patients who received elosulfase alfa developed neutralizing antibodies (Nab).

In Trial MOR004 and its extension MOR005, TAb was present by Week 4 in all 58 patients who received the QW regimen. All patients who received the QOW regimen developed TAb by Week 16. All elosulfase alfa treated patients, except one, (>98%) developed and sustained high TAb titer levels over 72 weeks of treatment. The majority of patients (96%) who received the QW regimen developed NAb by Week 16, compared to 84% of patients on QOW regimen. The proportion of patients positive for NAb decreased slightly by the end of Trial MOR004. That is approximately 87% of patients who received the QW regimen and 80% of patients who received the QOW regimen had NAb present at week 24 of treatment. These percentages declined further by week 72 of treatment, with 73% of patients on QW and 71% of patients on QOW remaining positive for NAb. NAb inhibits cellular uptake of elosulfase alfa by preventing drug binding to the cation-independent mannose-6-phosphate receptor of the lysosome. Because the majority of patients had persistently high titers of TAb and was NAb positive, it is difficult to determine the true impact of these antibodies on efficacy measures and the reduction in urine keratan sulfate (uKS).

The IgE antibody assay, itself, was found to be problematic with regard to sensitivity and, therefore, the interpretation of IgE antibody is limited. IgE antibodies against elosulfase alfa were detected in < 10% of treated patients. IgE positivity has not been consistently related to anaphylaxis, hypersensitivity reactions and/or treatment withdrawal.

Curiously, 20% of patients were observed to have pre-treatment anti-drug antibodies. Their anti-drug antibody levels increased with treatment, but there was no discernable impact on outcome measures.

Further discussion of immunogenicity results from the elosulfase alfa clinical trials is found in the full review by Dr. J. Wang, Immunology.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Adverse events by dose of treatment are described above in Section 7.3.

7.5.2 Time Dependency for Adverse Events

Adverse events by duration of treatment are described above in Section 7.3.

7.5.3 Drug-Demographic Interactions

There were some appreciable differences in AE incidence by age, gender and race/ethnicity. The safety population is mostly composed of pediatric patients (83%), with patients aged 5-11 years-old (53%) representing the predominant subset. Patients aged 0-5 years (n=16) demonstrated the highest overall AE incidence (100%) and drug-related AE incidence (75%). Those aged 5-11 years-old have an overall AE incidence of 80% and a drug-related AE incidence of 55%. Both of these age groups have similar incidence of overall SAEs and drug-related SAE. The AE incidences show a decreasing trend with increasing age. Refer to Table 32.

The safety population consisted of approximately equal number of male and female patients; however, the overall AE incidence and drug-related AE incidence were almost 20% higher in females than those in males. The incidence pattern switches for SAE, where more males (22%) experienced SAEs compared to females (14%). Both genders have a similar rate of drug-related SAEs. Refer to Table 32.

Consideration of race and AE incidence rate does not appear to show a remarkable difference for overall AEs or drug-related AEs. However, SAE incidence is greater (26%) in Asian patients when compared to that of White patients (15%) and Other race patients (15%). Drug-related SAE incidence rate in Asian patients is two times that of White patients. A small number of Black patients precludes meaningful interpretation of the AE incidence rates. Non-Hispanic patients appear to have higher incidences of SAEs, drug-related SAEs and drug-related AEs when compared to patients of Hispanic ethnicity. Refer to Table 32.

Table 32: Adverse Event Incidence by Age, Gender, and Race/Ethnicity in Patients Receiving Elosulfase Alfa 2.0 mg/mg QW in the Total Safety Population

Incidence: n (%)					
Age Group	**0 to <5 (n=16)**	**5 to <12 (n=117)**	**12 to <19 (n=50)**	**>=19 (n=39)**	**Total (n=222)**
AE	16 (100.0%)	93 (79.5%)	34 (68.0%)	28 (71.8%)	171 (77.0%)
Drug-Related AE	12 (75.0%)	64 (54.7%)	21 (42.0%)	19 (48.7%)	116 (52.3%)
SAE	4 (25.0%)	27 (23.1%)	5 (10.0%)	3 (7.7%)	39 (17.6%)
Drug-Related SAE	1 (6.3%)	7 (6.0%)	1 (2.0%)	0 (0.0%)	9 (4.1%)
AE Leading to Discontinuation	0	0	0	0	0
Death	0	0	0	0	0

Gender	**Male (n=105)**	**Female (n=117)**	**Total (n=222)**
AE	71 (67.6%)	100 (85.5%)	171 (77.0%)
Drug-Related AE	42 (40.0%)	74 (63.2%)	116 (52.3%)
SAE	23 (21.9%)	16 (13.7%)	39 (17.6%)
Drug-Related SAE	4 (3.8%)	5 (4.3%)	9 (4.1%)
AE Leading to Discontinuation	0	0	0
Death	0	0	0

Race and Ethnicity	**Asian (n=53)**	**Black or African American (n=4)**	**White (n=146)**	**Other (n=19)**	**Not Hispanic or Latino (n=180)**	**Hispanic or Latino (n=42)**	**Total (n=222)**
AE	43 (81.1%)	3 (75.0%)	113 (77.4%)	12 (63.2%)	141 (78.3%)	30 (71.4%)	171 (77.0%)
Drug-Related AE	31 (58.5%)	2 (50.0%)	75 (51.4%)	8 (42.1%)	101 (56.1%)	15 (35.7%)	116 (52.3%)
SAE	14 (26.4%)	0 (0.0%)	22 (15.1%)	3 (15.8%)	37 (20.6%)	2 (4.8%)	39 (17.6%)
Drug-Related SAE	4 (7.5%)	0 (0.0%)	5 (3.4%)	0 (0.0%)	9 (5.0%)	0 (0.0%)	9 (4.1%)
AE Leading to Discontinuation	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

Not applicable.

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Other than nonclinical study data, there is no clinical information regarding the safety of elosulfase alfa during pregnancy. No pregnant MPS IVA patients were enrolled in clinical trials.

7.6.3 Pediatrics and Assessment of Effects on Growth

An open-label trial (MOR007) is being conducted in 15 patients less than 5 years of age (mean 3 years, range 9 months to 4.9 years) treated with 2 mg/kg of elosulfase alfa QW. Half of the patients were male (n=7). Ten (68%) patients were White, four (27%) were Asian and one (7%) was Other race. The most common adverse reactions experienced by patients receiving elosulfase alfa included vomiting (80%), pyrexia (73%), and cough (53%). Four patients experienced at least one hypersensitivity reaction: moderate hypersensitivity reactions (n=2), urticaria (n=2), mild wheezing (n=1). The two patients with moderate hypersensitivity reactions were managed with discontinuation of the infusion and treatment with IV antihistamine and IV corticosteroids. One of these two patients (Patient 0021-7013) experienced severe hypersensitivity reactions of urticaria, hypotension, and tachycardia. The patient was hospitalized due to the persisting tachycardia, however, the event resolved the next day. The patient continued to receive her next scheduled dose of elosulfase alfa.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of elosulfase alfa overdose have been reported. Elosulfase alfa has no known potential for drug abuse. No studies were conducted to investigate the effect of withdrawal or rebound.

7.7 Additional Submissions / Safety Issues

In the 120-day safety update, additional AEs were reported.

- Common AEs were not different from those already reported above.
- Cases of hypersensitivity reaction were updated to 77 cases with eye swelling (2%) and erythema (2%) now commonly occurring in four or more patients.
- No new drug-related SAEs are presented in the 120-day safety update.

8 Postmarket Experience

There is no postmarketing experience because the drug product has not yet been approved in any country.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

- Include anaphylaxis boxed warning
- Section 5 Warnings and Precautions: change (b) (4) reactions to "hypersensitivity" reactions, delete the separate section on (b) (4) add new section on the risk of acute respiratory complications during administration
- Section 6.1 Adverse Reactions: Table should only include drug-related AEs, add paragraph with additional adverse reactions from QOW treatment group
- Section 14 Clinical Studies – Table should only have 6MWT results, (b) (4)

Medical Officer Comments:
For the Clinical Studies revisions in section 14 of the FPI, this reviewer believes graphical data may be misleading of the actual clinical benefit a patient expect, since baseline performance on the 6MWT appears to be an important factor.

Otherwise, results of the (b) (4) are noncontributory to the demonstration of efficacy and the (b) (4) results cannot be correlated to clinical outcome.

9.3 Advisory Committee Meeting

The Division held an Advisory Committee Meeting on November 19, 2013.
Below is a summary of questions to the committee and committee member responses.

1. **DISCUSSION:** Does a change in 6-minute walk test (6MWT) from baseline to Week 24 adequately evaluate treatment benefit in patients with Mucopolysaccharidosis Type IVA (Morquio A syndrome)?

The majority of the Advisory Committee (AC) members found the 6MWT to be adequate for evaluating MPS IVA patients. They noted, that as an integrated measure, the 6MWT was able to show change in this heterogeneous patient population. Those who found the 6MWT inadequate, however, noted that it is only one measure and not able to assess multiple factors that affect patients' function (i.e., key disease symptoms of pain and fatigue). AC members were concerned about the long term durability of effect with elosulfase alfa treatment.

2. **DISCUSSION:** Are there other measures of treatment benefit that could be assessed in patients with MPS IVA?

AC members believed that additional outcome measures that focused on other facets of the MPS IVA disease, as well as quality of life and biomarker activity, would provide additional evidence of treatment benefit. The suggested additional outcomes included change of pain and fatigue, change in the use of supportive therapies, time to orthopedic surgery, muscle strength testing, range of motion assessment, radiographic imaging of skeletal progression, change in growth, change in sleep and activity levels, and assessment of child health and family functioning via quality of life questionnaires. Assessment of the change in N-acetylgalactosamine-6-sulfatase (GALNS) enzyme activity from both leukocytes and affected tissues was suggested.

3. **VOTE:** Does the totality of clinical data support the effectiveness of elosulfase alfa for treatment of MPS IVA? When responding, consider whether the magnitude of treatment difference observed in the 6MWT and the 3-minute stair climb test (3MSCT) represents a clinically meaningful benefit in MPS IVA patients.

A. Yes, the data support effectiveness in all MPS IVA patients.
B. Yes; however, the data only support effectiveness in a subgroup of MPS IVA patients. *Please describe that subgroup in your response*.
C. No, the data do not support effectiveness in MPS IVA patients.

AC members voted ***A: 13 B: 7 C: 1***

AC members who voted "B" noted that there were some patients who did not respond and benefit is not known for those MPS IVA patients who were not enrolled in the pivotal trial.

The AC member voting "C" was concerned regarding the convergence of treatment effect of all treatment arms at 72 weeks such that there was no difference in treatment whether the treatment duration was 24 weeks or 72 weeks.

4. **VOTE:** Does this application raise concerns about safety findings in elosulfase alfa in MPS IVA patients?

AC members voted ***YES: 5 NO: 16 ABSTAIN: 0***

AC members who voted "Yes" cited the risk of anaphylaxis and hypersensitivity, as well as the risks associated with central line placement for chronic drug administration. Those who voted "No" commented that the benefits outweigh the risks.

5. **VOTE:** Do you recommend approval of elosulfase alfa for the treatment of MPS IVA?

A. Yes, I recommend approval for all MPS IVA patients.
B. Yes, I recommend approval for a subgroup of MPS IVA patients. *Please describe that subgroup in your response.*
C. No, I do not recommend approval.

AC members voted ***A: 19 B: 1 C: 1***

The majority of AC members felt that elosulfase alfa should be approved for all MPS IVA patients. The member who voted "B" commented that the drug is safe and efficacious in a large number of patients, but the data did not show that the drug would be efficacious in the group of patients that are able to walk more than 200 meters. The member voting "C" expressed uncertainty over long term efficacy of the drug.

9.4 Supplemental Materials

- 9.4.1 Narratives of Serious Adverse Events
- Table 33: Descriptions of Anaphylaxis Events

9.4.1 Narratives of Serious Adverse Events

- **Patient MOR002-0119-2007 - anaphylaxis**

Patient 0119-2007 experienced a Type 1 hypersensitivity reaction on Week 11 during the tenth infusion of elosulfase alfa 0.1 mg/kg QW. The patient had not been pre-treated with an antihistamine or an antipyretic. The infusion was initiated at a rate of 1.4 mL/hr in accordance with the protocol. The rate was increased to 18.5 mL/hr after 1 hour. Five minutes after the rate increase, the patient experienced symptoms of generalized urticaria, edema, and difficulty breathing with stridor and wheezing. The infusion was immediately discontinued and the patient was treated with oxygen, hydrocortisone, adrenaline, and chlorpheniramine maleate. Tryptase and complement levels obtained at the time of the reaction were normal, and O2 was 100%. Total IgE was elevated and a positive drug-specific IgE was obtained at the time of the reaction. The event resolved 1 day after onset. The patient discontinued from the trial after Week 11. The protocol was amended following this event to require that all patients be pre-treated with an antihistamine, and that antipyretics would be administered at the discretion of the investigator.

- **Patient MOR002-0121-2003 – severe hypersensitivity and anaphylaxis**

Patient 0121-2003 experienced recurrent reactions primarily characterized by skin (urticaria) and gastrointestinal (abdominal pain, vomiting) symptoms. This patient first experienced hypersensitivity reaction associated with infusions of elosulfase alfa 1.0-mg/kg QW on Weeks 13 through 15. Symptoms included retching, abdominal pain, and reduced oxygen saturations. On Week 27, the patient experienced reactions associated with infusion of elosulfase alfa 2.0-mg/kg QW consisting of pyrexia, shivering, tachycardia, and vomiting. On Week 36, the patient experienced retching and abdominal pain during the elosulfase alfa infusion. During this period the patient had several samples tested for drug-specific IgE, which were negative. As specified in the protocol, starting at Week 37, the dose was decreased to elosulfase alfa 1.0-mg/kg/qw. The patient continued to experience reactions including urticaria, retching, and vomiting through Week 45. Two sets of tryptase levels obtained in conjunction with reactions were normal; total IgE was elevated at Week 39. Modification of the infusion rate and alterations in medications did not prevent the recurrence of reactions. The patient discontinued treatment after Week 45 at the principal investigator's discretion, but remained enrolled in the trial.

- **Patient MOR004-1075-4007 - anaphylaxis**

Patient 1075-4007 is a 6-year-old male who experienced a severe, serious event of anaphylaxis. No history of previous drug allergies or anaphylactic reactions was reported. He received his first infusion of treatment with elosulfase alfa 2.0 mg/kg/qow on (b) (6) Pre-infusion vital signs on that date included BP 100/59 mmHg, pulse 102 bpm, and respiratory rate 22/min. Pre-medications included oral clemastine and paracetamol. On 28 July 2011, about 2 hours after the infusion began, he

complained of abdominal pain and mild nausea; vital signs were stable. He developed urticaria (mostly on the face and abdomen), severe itching, restlessness, and swollen eyes and mouth. Vital signs at that time were BP 121/86, pulse 142 bpm, and respiratory rate 28. Treatment for the event included IV clemastine and IV prednisone. The study treatment infusion was stopped. He had a low blood pressure reading of 80/53 mm Hg and was treated with IM epinephrine and an IV fluid bolus. His oxygen saturation levels never dropped below 94-95%. He was admitted to the hospital for overnight monitoring. The event of anaphylaxis was considered resolved later that day, and the patient was stable overnight. The patient remained on the trial.

- **Patient MOR004-0121-4139 – severe reaction during infusion**

Patient 0121-4139 is a 5-year-old male who experienced a moderate, serious event of vomiting. He received his first infusion of elosulfase alfa 2.0 mg/kg/week on (b) (6) During the trial, the patient experienced several non-serious mild or moderate events of stomach ache, as well as a moderate event of nausea, all of which occurred on infusion dates. Pre-medication for the infusions reportedly included hydrocortisone. On 3 May 2012, pre-infusion vital signs were BP 117/64 mmHg, pulse 116 bpm, temperature 36.8°C, and respiratory rate 26. During the study treatment infusion, the patient developed tachycardia and abdominal pain; the infusion was not interrupted or slowed, and no treatment for these events was reported. During infusion, his pulse had risen to 160 and his temperature was 37.3°C. He vomited a large amount, and two small areas of urticaria were noted on his left arm. The patient was hospitalized, and treatment included IV chlorphenamine and IV hydrocortisone. The event resolved later that day. No action was taken with study treatment as a result of the event, and the patient remained on the trial.

- **Patient MOR004-0020-4141– severe hypersensitivity**

Patient 0020-4141 is an 18-year-old male who experienced a severe, serious event of hypersensitivity. He received his first infusion of elosulfase alfa 2.0 mg/kg/week on (b) (6) The patient developed a mild, non-serious upper airway infection on 23 March 2012; treatment included salbutamol, and the event remained ongoing. The last dose prior to event onset was administered on 27 March 2012. On 27 March 2012, the patient's pre-infusion vital signs were BP 123/83 mmHg, pulse 79, and temperature 36.3°C. Two and one half hours after infusion began, the patient developed a severe hypersensitivity reaction, with symptoms of vomiting, shivering, and paleness. The infusion was stopped, and vital signs at that time included BP 147/99, pulse 111, and temperature 37.4°C. The patient developed upper airway obstruction, tachycardia (pulse 127), and hypertension (BP 140/100). Treatment included IV ranitidine, prednisolone, epinephrine, fluids, IV paracetamol, and inhalation therapy. The patient showed slow improvement and he was taken to the immediate care station for overnight observation. He experienced no further symptoms, and the event was considered resolved the next day. The patient received his next study treatment infusion as scheduled, and experienced no further infusion-associated reactions for the remainder of the trial.

- **Patient MOR004-0021-4005 - anaphylaxis**

Patient 0021-4005 is a 5-year-old female (age at time of enrollment in MOR-004) who experienced a serious grade 4 anaphylactic reaction. She started treatment in MOR-004 on placebo on (b) (6), and she received her first dose of elosulfase alfa 2.0 mg/kg QOW in MOR-005 on 23SEP2011. On 13JAN2012, she developed difficult breathing, elevated blood pressure, and low oxygen saturation (90% on 15L O2). Treatment included epinephrine, oxygen, hydrocortisone, and chlorphenamine. The event resolved about 20 minutes after the onset of symptoms, and patient remained on the trial. The investigator considered the event of anaphylactic reaction to be probably related to elosulfase alfa.

- **Patient MOR100-0119-2004 - hypersensitivity**

Patient 0119-2004 is an 11-year-old female (age at time of enrollment in MOR-100) who experienced serious event of grade 1 malaise. She received her first infusion of elosulfase alfa 2.0 mg/kg QW in MOR-100 on (b) (6). On 06APR2011, the patient's pre-infusion vital signs included BP 105/72 mmHg, pulse 104, and temperature 36.9°C. Approximately 2 hours and 20 minutes into the infusion, she began to feel faint, with a headache, abdominal pain, pallor, and a clammy feeling. Vital signs were normal, and the infusion was interrupted. No treatment for the event was reported, and it was considered resolved on that same date. The elosulfase alfa infusion was not restarted, but the patient returned for her next scheduled infusion without a recurrence of the event and she remained on the trial.

- **Patient MOR100-0119-2010 - hypersensitivity**

Patient 0119-2010 is an 11-year-old female (age at time of enrollment in MOR-100) who experienced a serious grade 2 event of infusion site reaction. She received her first infusion of elosulfase alfa 2.0 mg/kg QW in MOR-100 on (b) (6). On 06APR2011, her infusion was started at the rate of 3 ml/hr. After receiving approximately 0.9 ml, it was noted that the infusion site was red and swollen (but without any pain); the size of the red and swollen area was about 2 cm × 2 cm, and there was significant induration. The infusion was interrupted, and the cannula was withdrawn. Because the patient was generally difficult to cannulate, the infusion was not restarted. The plastic surgery team was consulted, and the site was irrigated with normal saline. Following the event, the patient did not return for her next study treatment infusion until 27APR2011. At that time, she was re-evaluated and the event was noted to have resolved. A subsequent infusion was administered without a recurrence of the event, and the patient remained on the trial. The investigator assessed the event of infusion site reaction as possibly related to elosulfase alfa.

- **Patient MOR100-0119-2013- hypersensitivity**

Patient 0119-2013 is a 6-year-old male (age at time of enrollment in MOR-100) who experienced serious event of grade 2 pyrexia. He received his first infusion of elosulfase alfa 2.0 mg/kg QW in MOR-100 on (b) (6). On 20APR2011, the

patient's pre-infusion vital signs included temperature 36.9°C. During the infusion, the patient experienced non-serious grade 1 port pain; the infusion was interrupted and not restarted. That evening, the patient was hospitalized with a viral infection, temperature of 39.4°C, vomiting, and a rash on the torso, arms, and legs. Blood and urine cultures were negative. Treatment for the event included piperacillin/tazobactam. The Port-a-Cath was removed on 21APR2011, but the patient was still symptomatic (with fever, vomiting, and diarrhea) on 22APR2011. Additional treatment included teicoplanin. The event of pyrexia was considered resolved as of 28APR2011; the patient was discharged from the hospital on (b) (6). He received his next dose of study treatment on 25MAY2011 and remained on the trial. The investigator assessed the event of infusion site reaction as possibly related to elosulfase alfa.

- **Patient MOR100-0121-2005- hypersensitivity**

Patient 0121-2005 is a 9-year-old female (age at time of enrollment in MOR-100) who experienced serious events of grade 3 pyrexia and hypertension. The patient's pre-infusion vital signs reportedly included a temperature of 37.4°C; pre-infusion blood pressure was not reported. The infusion was started; she developed a fever to 39.1°C accompanied by rigors and a cough. The infusion rate was reduced and she was given paracetamol, but the fever and rigors persisted. About 15 minutes after the onset of symptoms, her vital signs reportedly were pulse 137 bpm, BP 137/104 mmHg, and temperature 39.4°C. The infusion was stopped. Following discontinuation of the infusion, the patient's temperature decreased to 37.5°C, her blood pressure decreased to 111/88, and her cough improved. A chest X-ray revealed no areas of consolidation or other signs of lower respiratory tract infection. Laboratory results reportedly included white blood count 6.8 × 109/L (neutrophils 4.8 × 109/L). The event was considered resolved later that day. The investigator assessed the event of pyrexia as probably related to elosulfase alfa. The Grade 3 hypertension during infusion was assessed as probably related to elosulfase alfa.

- **Patient MOR100-0121-2012- hypersensitivity**

Patient 0121-2012 is a 6-year-old female (age at time of enrollment in MOR-100) who experienced serious events of grade 2 inflammation, grade 1 and grade 2 flushing, and grade 2 infusion site reaction (on two separate occasions). She received her first infusion of elosulfase alfa 2.0 mg/kg QW in MOR-100 on (b) (6). On 15JUN2011, the patient developed a localized inflammation with intense redness after receiving only about 9 mL of the infusion. The IV was removed, and a new IV was placed in a larger vein in the other arm. The infusion was resumed, but after the patient had received approximately 40% of the planned total, localized swelling, redness and tenderness developed. She showed no significant signs of hemodynamic compromise, but did have temporarily lowered blood pressure which resolved after the infusion was stopped. The patient was kept in the hospital for an additional 6 hours to ensure that the event would resolve. The event of serious grade 2 inflammation was considered resolved as of 18JUN2011. The patient remained on the trial; prior to her next scheduled infusion on 22JUN2011, she was premedicated with oral prednisolone

and the infusion was run at a slower rate. The patient tolerated this infusion without incident, though she did develop small (5 mm) sites of erythema on her wrists bilaterally. The patient started receiving concomitant prednisolone on 22JUN2011. On 29JUN2011, pre-infusion vital signs were BP 107/58 mmHg, pulse 88, and temperature 36.7°C. Approximately 2 hours into the infusion, the patient developed erythematous spots on the back of her neck, left arm, and both hands. No adjustment was made to the infusion. Approximately 6 hours into the infusion, she developed red facial flushing while receiving her saline fluid flush. No treatment was given, and the infusion was completed. While under post-infusion observation, the patient's temperature rose to 37.4°C, and she was given paracetamol. The flushing had improved but was still present when the patient was sent home, and it was considered resolved the next day. On 06JUL2011, the infusion was started following premedication with ranitidine and prednisolone. Approximately 80 minutes into the infusion, the patient developed swelling at the infusion site and transient facial flushing. Her pulse dropped from a pre-infusion rate of 82 bpm down to 70, but no respiratory or hemodynamic symptoms were noted. There was no IV site extravasation. Treatment included chlorphenamine. The infusion was stopped for the day, and the events of infusion site reaction and flushing resolved later that day. On 26OCT2011, the patient was premedicated with montelukast and ranitidine prior to the infusion. After approximately 20 mL had been infused, she developed swelling without redness at the infusion site. There was no significant change to her vital signs during the course of the event. The infusion was interrupted, and the event resolved later that day. While the patient remained on the trial and continued to receive weekly elosulfase alfa infusion, she also continued to experience non-serious events during infusions, some of which caused infusions to be interrupted or infusion rates to reduced. The investigator considered the events of inflammation (15JUN2011), flushing (29JUN2011) and infusion site reaction (26OCT2011) as probably related to elosulfase alfa, and the events of infusion site reaction (06JUL2011) and flushing (06JUL2011) as possibly related to elosulfase alfa.

- **Patient MOR007-0021-7013- hypersensitivity (from 120 day report)**

Patient 0021-7013 is a 4-year-old female who experienced a serious grade 2 event of hypersensitivity. She received her first weekly infusion of elosulfase alfa 2.0 mg/kg on (b) (6). On 23AUG2012, the patient's pre-infusion vital signs included a temperature of 37.6°C, BP of 118/85 mmHg, and a pulse of 100. The infusion was started, and following infusion rate increase to 6 ml/hr, she developed a sudden hypersensitivity reaction, with tachycardia, urticarial rash, and a feeling of agitation or distress. Vital signs were included BP 104/65, pulse 152, temperature 36.4°C, and oxygen saturation 97%. The infusion was discontinued, and treatment for the event included IV chlorpheniramine and IV hydrocortisone. The patient's symptoms improved following this treatment, but because she remained tachycardic she was admitted overnight to the hospital for observation. The event was considered resolved the next day, and the patient received her next scheduled dose of elosulfase alfa on 30AUG2012 without a recurrence of the event.

Table 33: Descriptions of Anaphylaxis Events in Clinical Trials

Patient	Age Sex	Race	Treatment Regimen	Events/Symptoms	Time to Onset	Premedication	Intervention
MOR002-0119-2007†	13 M	Mixed	QW	Type I hypersensitivity/ generalized urticaria, edema, stridor, wheezing	10th infusion (65 minutes following start)	None	oxygen, hydrocortisone, adrenaline, and chlorpheniramine
MOR002-0121-2003	7 M	Asian	QW	Generalized rash	39th infusion (100 minutes following start)	Cetirizine, acetaminophen	chlorphenamine
MOR002-0121-2003	7 M	Asian	QW	Infusion related reaction/ urticaria, hypotension	42nd infusion (80 minutes following start)	Hydroxyzine, hydrocortisone, acetaminophen	IV chlorphenamine, IV hydrocortisone
MOR002-0121-2003	7 M	Asian	QW	Drug eruption/urticarial rash and retching	43rd infusion (65 minutes following start)	Acetaminophen, prednisolone, cetirizine	IV chlorphenamine, IV hydrocortisone
MOR002-0121-2003	7 M	Asian	QW	Infusion related reaction/ urticarial skin reaction of the face and neck, widespread rash and vomiting	44th infusion (85 minutes following start)	Acetaminophen, prednisolone, ranitidine, cetirizine	IV chlorphenamine, IV hydrocortisone
MOR002-0121-2003*	7 M	Asian	QW	Infusion related reaction/ generalized urticarial rash, vomiting, oxygen desaturation	45th infusion (27 minutes following start)	Acetaminophen, prednisolone, montelukast, cetirizine	IV chlorphenamine, IV hydrocortisone

Patient	Age Sex	Race	Treatment Regimen	Events/Symptoms	Time to Onset	Premedication	Intervention
MOR004-0020-4141	18 M	White	QW	Hypersensitivity/ upper airway obstruction, hypertension, tachycardia, vomiting, shivering,	5th infusion (2.5 hours after the start)	Cetirizine	Prednisolone, epinephrine, inhalation therapy, IV fluids, IV
MOR004-0021-4005	5 F	White	Pbo-QOW	Anaphylaxis/ dyspnea, oxygen desaturation, hypertension	17th infusion in MOR-005 (approximately 2 hours after start)	Cetirizine, acetaminophen, ranitidine, montelukast	15L oxygen, epinephrine, hydrocortisone, chlorphenamine
MOR004-0021-4103	5 F	White	QW	Cough, facial erythema, oxygen desaturation	34th infusion (13 minutes following start)	Prednisolone, hydroxyzine, ranitidine, acetaminophen	Oxygen, chlorphenamine
MOR004-0050-4063	9 F	White	QW	Throat tightness, nausea, shivering, dry throat and mouth	16th infusion (45 minutes after start)	Ranitidine, acetaminophen, diphenhydramine	IV diphenhydramine
MOR004-0109-4025	5 F	White	QW	Urticaria of face and abdomen, abdominal pain	4^{th} infusion	Diphenhydramine, cetirizine	IV diphenhydramine
MOR004-0109-4025	5 F	White	QW	Urticaria – generalized, abdominal pain, headache	38th infusion (2.5 hours after start)	Diphenhydramine, acetaminophen, ranitidine	oral diphenhydramine, acetaminophen, and ondansetron
MOR004-0109-4028	7 M	White	QOW	Cough, flushing, erythematous rash	5th infusion in MOR-005 (75 minutes following start)	Cetirizine	IV diphenhydramine

Patient	Age Sex	Race	Treatment Regimen	Events/Symptoms	Time to Onset	Premedication	Intervention
MOR004-0111-4019	11 F	White	QW	Cyanosis, hypotension, vomiting, shivering, fatigue, fever, headache	26th infusion (80 minutes following start	Betamethasone, EMLA patches, acetaminophen, hydroxyzine, ondansetron	acetaminophen, hydroxyzine, ibuprofen, methylprednisolone, and IV fluids
MOR004-0121-4139	5 M	Asian	QW	Urticaria, vomiting, hypotension	9th infusion (timing not reported)	Hydrocortisone, cetirizine	chlorphenamine
MOR004-1017-4016	7 F	White	QOW	Dyspnea, flushing	15th infusion (40 minutes following start)	Cetirizine, acetaminophen	acetaminophen
MOR004-1075-4007	6 M	White	QOW	Anaphylactic reaction/ uricaria, pruritus, facial edema, tachycardia, nausea, abdominal pain	7th infusion (48 minutes following start)	Clemastine, acetaminophen	Oral and IV clemastine, IV prednisone. IM epinephrine, IV fluids
MOR004-1075-4007	6 M	White	QOW	Anaphylactic reaction/ urticaria, itching, restlessness, facial edema, hypotension	47th infusion (70 minutes following start)	Cetirizine, acetaminophen	IV antihistamines and IV steroids
MOR004-1075-4050	5 M	White	QW	Cough, flushing	11th infusion (time from start not clear)	Clemastine, acetaminophen	None
MOR004-1159-4109	12 M	Asian	QW	Cough, rash, dyspnea	45th dose of drug (2.5 hours following start -- 4th dose on QW regimen	Loratadine	oxygen

Patient	Age Sex	Race	Treatment Regimen	Events/Symptoms	Time to Onset	Premedication	Intervention
MOR004-1159-4117	16 F	Asian	QW	Urticaria, hypotension, vomiting	24th infusion (75 minutes following start)	Loratadine, hydrocortisone	Hydroxyzine
MOR004-1159-4117	16 F	Asian	QW	Anaphylactic reaction, allergic reaction, hypertension, tachycardia	25th infusion (75 minutes following start)	Loratadine, prednisolone	chlorphenamine, oxygen, hydroxyzine, loratadine, methylprednisolone
MOR004-1167-4068	9 F	Asian	QOW	Urticaria, chest discomfort, vomiting, tachycardia	5th infusion in MOR-005 (110 minutes following start)	Acetaminophen, hydroxyzine	oxygen, IV fluids, and IV chlorphenamine
MOR007-0018-7005	2 M	Asian	QW	Urticaria, abdominal pain	14th infusion (50 minutes after start)	Loratadine	diphenhydramine
MOR007-0018-7005	2 M	Asian	QW	Urticaria, abdominal pain	15th infusion (1 hour after start)	Loratadine	oral diphenhydramine
MOR008-0109-8106	7 F	White	QW	Vomiting, pallor, bradycardia, hypotension 2 days later: Urticaria	4th infusion (2.5 hours following start and 2 days after infusion)	Diphenhydramine	diphenhydramine, IV fluids, methylprednisolone, acetaminophen, and ondansetron

† Patient MOR002-0119-2007 was the first patient in the clinical development program to demonstrated anaphylaxis. Subsequent to this event, all patients received anti-histamine premedication, at minimum.
* Patient MOR002-0121-2003 was discontinued from further study treatment following his 45th infusion.

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/s/

TAMARA N JOHNSON
11/26/2013

JESSICA J LEE
11/26/2013

Memorandum of Consultation

BLA/IND	Document Date	Letter Date	Tracking #	Consult Date
125460/101234	March 29, 2013	July 24, 2013	467	August 6, 2013

Application: BLA 125460

Sponsor: BioMarin Pharmaceutical Inc.

Indication: Mucoplysaccharidosis IV Type A (MPS IV A)

Drug: BMN 110/ Elosulfase alfa

Class: Recombinant enzyme replacement /Biologic

To: ODE III/DGIEP

From: John T. Stinson, M.D., Medical Officer DBRUP

Through: Theresa Kehoe, M.D., Team Leader
Hylton Joffe, M.D. M.M.Sc. Division Director

Background

DGIEP is seeking advice regarding additional clinical outcome measures for patients with Morquio A syndrome. BLA 125460, currently under review, is for a potential recombinant therapy that replaces the enzyme for which these patients are deficient. Patients' improvement on the primary endpoint, the six-minute walk test, was statistically significant in the primary trial (MOR-004), although of indeterminate clinical significance. No improvement was seen on the secondary endpoint, the three-minute stair climb test endurance measure. DGIEP is concerned that these endpoints do not truly measure changes in musculoskeletal function as is needed for clinical benefit in this patient population. DGIEP asks DBRUP the following questions:

1) For the musculoskeletal deformities and symptoms of the MPS IV A population described above, please advise us on additional clinical outcome measures that may better demonstrate change in musculoskeletal function with treatment. For these additional clinical outcome measures, explain reliable methods used for measurement in clinical practice or research, the frequency of measurements, and over what interval one would expect to see change.
2) Provide your perspective of the relevance of the six-minute walk test and three-minute stair climb test to the MPS IV A population.

Morquio A syndrome

The sponsor is developing BMN 110 as an enzyme replacement therapy for the treatment of Mucoplysaccharidosis IV Type A (Morquio A syndrome, MPS IV A). Morquio A syndrome is an autosomal recessive inherited disorder classified in the group of mucopolysaccharide storage diseases. Presently, there are eleven different enzymatic defects associated with seven different types of mucopolysaccharidosis (Table 1). The lack of enzymatic activity leads to tissue-specific intracellular accumulation of substrates. MPS IV A is caused by gene mutations resulting in insufficient lysosomal enzyme N-acetylgalactosamine -6-sulfatase (GALNS). The enzyme hydrolyzes the sulfate moiety of the glycosaminoglycans (GAGs) keratan sulfate and chondroitin-6-sulfate. GALNS insufficiency results in blockage of the stepwise degradation of GAGs and their progressive and pervasive buildup in lysosomes in multiple organs and tissues leading to multisystem impairments and morbidities. There may be a range of residual GALNS activity due to attenuated mutations, and some have grouped cases into severe, intermediate, and mild categories. MPS IV A is generally a progressive disabling disorder for which no treatment, aside from supportive measures, is available. Precise epidemiological data are scarce, and the reported incidence is variable. Morquio A syndrome is estimated to occur in 1 in 200,000 to 300,000 live births in the US.

Table 1 Classification of Mucopolysaccharidoses

Type	Main Diseases	Deficient Enzyme	Accumulated Product(s)
MPS I	Hurler Syndrome	A-L-iduronidase	Heparan Sulfate Deramatan Sulfate
MPS II	Hunter Syndrome	Iduronate sulfatase	Heparan Sulfate Deramatan Sulfate
MPS III	Sanfilippo Syndrome A	Heparan sulfamidase	Heparan Sulfate
	Sanfilippo Syndrome B	N-acetylglucosaminidase	
	Sanfilippo Syndrome C	Acetyl-CoA:alpha-glucosaminide acetyltransferase	
	Sanfilippo Syndrome D	N-acetylglucosamine 6-sulfatase	
MPS IV	Morquio Syndrome A	Galactose-6-sulfate sulfatase	Keratan sulfate Chondroitin 6-sulfate
	Morquio syndrome B	Beta-galactosidase	Keratan sulfate
MPS VI	Maroteaux-Lamy Syndrome	N-acetylgalactosamine-4-sulfatase	Dermatan sulfate
MPS VII	Sly Syndrome	β-glucuronidase	Heparan sulfate Dermatan sulfate Chondroitin 4,6-sulfate
MPS IX	Natowicz Syndrome	Hyaluronidase	Hyaluronic acid

It is not possible to accurately differentiate between mucopolysaccharidosis types based on specific skeletal x-ray or neuroimaging characteristics. The primary clinical manifestation of Morquio A syndrome is progressive skeletal dysplasia (dysostosis multiplex), leading to frequent surgical procedures related to musculoskeletal or respiratory dysfunction[11]. The unique clinical manifestations of this disorder are attributable to the restricted tissue distribution of keratan sulfate (cornea, cartilage, nucleus pulposus, heart valves), in contrast to the much wider distribution of dermatan

sulfate and heparan sulfate whose accumulations lead to other types of mucopolysaccharidosis.

The specific mechanism by which excessive GAG storage results in the skeletal dysplasia unique to Morquio A syndrome remains unknown. Growth plate chondrocyte pathology in MPS IV A is characterized by vacuolar distention, defective differentiation, chaotic arrangement and poorly calcified matrix[20]. Bone cells, osteoblasts and osteoclasts appear unaffected. Anderson et al concluded that the cause of dwarfism lies primarily in the deficit in chondrocyte differentiation rather than abnormal bone formation[21]. Cartilage and heart valve spongiosa, the major therapeutic targets in MPS IV A, are largely avascular, and are as such challenging to penetrate with therapeutic compounds.

Findings may include growth retardation, brevicollis, kyphoscoliosis, genu valgum, joint hypermobility and pectus carinatum. The most common initial symptoms reported include bone deformity (knee, spine, and chest), short stature and abnormal gait[11]. A cross-sectional baseline analysis of 325 MPS IV A patients, estimated to represent 10% of the global MPS IV A population, showed that more than 90% had these findings[19]. Spinal abnormalities were common; kyphoscoliosis was present in 85%, odontoid dysplasia in 65%, excessive lumbar lordosis in 56%, and cervical spine instability in 49%. Pectus carinatum with barrel chest was present almost universally[19].

Odontoid hypoplasia is the most critical skeletal feature to be found in any patient with Morquio A syndrome. Odontoid hypoplasia in combination with ligamentous laxity and extradural mucopolysaccharide deposition results in atlantoaxial subluxation, cervical myelopathy and possibly death. The skeletal dysplasia, short stature, and joint abnormalities all contribute to diminished mobility. Many patients are non-ambulatory by their teenage years.

GAG accumulation may occur at multiple sites including respiratory, circulatory and central nervous systems, skeleton, eyes, ears, joints, skin and teeth. Generally, Morquio A patients exhibiting a severe phenotype do not survive beyond the second or third decade of life, primarily due to cervical instability and pulmonary compromise. In contrast, patients with an attenuated phenotype have been reported to survive into the seventh decade.

Patients may experience both restrictive lung disease due to thoracic deformity and obstructive disease due to laryngeal narrowing and abnormalities of the trachea and bronchi. By 5 years of age, Morquio A patients often require surgical procedures such as adenoidectomy and tonsillectomy. Patients are often dyspnoeic and subject to recurrent respiratory infections and potentially to respiratory failure. Associated symptoms may include valvular disease, hearing loss, and visual impairment due to corneal clouding and cataract formation. Intelligence is normal.

The mucopolysaccharidoses, including MPS IV A, are characterized by a clinical heterogeneity encompassing a range of age and disease severity. With over 175 identified mutations in the GALNS gene, the progression of symptoms in MPS IV A is variable and

the wide phenotypic spectrum of MPS IV A makes it a challenging disorder to diagnose. Clinical suspicion raised by radiographic abnormalities may be supported by quantitative and/or qualitative testing of urinary GAG levels of keratin sulfate, but diagnosis requires confirmation of GALNS deficiency in white blood cells or fibroblasts (<5% of enzyme activity in normal controls), or mutation analysis showing the presence of mutations in both alleles.

BMN 110

BMN 110 is a recombinant form of human N-acetylgalactosamine-6-sulfatse (rhGALNS). BMN 110 is produced in a genetically engineered Chinese Hamster Ovary mutant cell line that over-expresses the cDNA encoding for the full human GALNS protein. The sponsor reports this to be identical to the naturally occurring human lysosomal enzyme with respect to the amino acid sequence and N-linked glycosylation sites. BMN 110 is intended to provide exogenous GALNS that will be taken up into the lysosomes and increase catabolism of GAGs keratin sulfate and chondroitin-6-sulfate. Uptake of BMN 110 by cells into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of BMN 110 to the cation-independent mannose-6-phosphate receptor.

MOR-004 Protocol Synopsis

This was a Phase 3, randomized, double-blind placebo-controlled multinational clinical trial to evaluate the efficacy and safety of BMN 110 2.0 mg/kg/ week and 2.0 mg/kg/ every other week (qow) in patients with MPS IV A. The primary objective was to evaluate the ability of BMN 110 administered intravenously 2.0 mg/kg/week and 2.0 mg/kg/qow to enhance endurance in subjects with MPS IV A, as measured by increase in meters walked in the six-minute walk test (6MWT) from Baseline to Week 24 compared to placebo.

The secondary objectives of the trial were the following:

- To evaluate the 2 dosage regimens of BMN 110 compared with placebo to enhance endurance in MPS IV A subjects, as measured by increase in stairs climbed per minute in the three-minute stair climb test (3MSCT) from Baseline to Week 24.
- To evaluate the ability of the two dosage regimens of BMN 110 to reduce normalized urine keratan sulfate (KS) levels in subjects with MPS IV A compared to placebo.

The tertiary objectives of the trial were:

- To determine the pharmacokinetics parameters of the 2 dosage regimens of BMN 110 in a subset of subjects with MPS IV A.
- To evaluate the ability of the 2 dosage regimens of BMN 110 compared with placebo, to improve respiratory function as measured by percentage increase in pulmonary function tests from Baseline to Week 24.

- To evaluate the effect of the 2 dosage regimens of BMN 110 compared with placebo, on biochemical markers of inflammation and bone and cartilage metabolism.
- To evaluate the effect of the 2 dosage regimens of BMN 110, compared to placebo, on quality of life as assessed by the MPS Health Assessment Questionnaire (HAQ).

Reviewer Comment: *The MPS HAQ is a 52-question instrument to evaluate functional capabilities and performance in children and adults with MPS. It was originally developed to assess the self care and mobility skills of patients with MPS I and the sponsor acknowledges that it is not optimally designed to capture changes in these domains as perceived specifically by MPS IV A patients, despite the shared characteristics of these two disorders.. The MPS HAQ assessed self-care, mobility skills, and the extent of required caregiver assistance in the performance of these activities. The MPS HAQ was administered at Baseline, Week 12, Week 24, and within one week of early withdrawal and was to be completed by a parent or guardian for subjects younger than 14 years.*

- To evaluate the 2 dosage regimens of BMN 110 compared with placebo on hearing as measured by audiometry.
- To evaluate the effect of the 2 dosage regimens of BMN 110, compared with placebo, on cardiac valve function as measured by echocardiogram.
- To evaluate the effect of the 2 dosage regimens of BMN 110 compared to placebo, on corneal clouding as assessed by physical examination.

Exploratory objectives

- To obtain baseline cardiac, pulmonary, and anthropometric measurements and monitor them to allow documentation of long term impacts of BMN 110 on these clinical disease markers.

Inclusion Criteria

Individuals eligible to participate in this study must have met the following criteria:

- a clinical diagnosis of MPS IV A based on clinical signs and symptoms of MPS IV A and documented reduced fibroblast or leukocyte GALNS activity or confirmatory genetic testing
- $\geq$ 5 years of age,
- had an average screening 6MWT distance $\geq$ 30 and $\leq$ 325 meters,
- were willing to use an acceptable method of contraception during the trial (if sexually active),
- Willingness and ability to provide informed consent (by subjects or their legally authorized representatives

Reviewer Comment: *While the sponsor maintains that the patient population enrolled in MOR-004 is broadly reflective of that in the general MPS IV A population, the proportion of subjects included with the severe MPS IV A phenotype is not specified.*

Exclusion Criteria

Individuals who met any of the following exclusion criteria were not eligible to participate in the study:

- Previous hematopoietic stem cell transplant
- Previous treatment with BMN 110
- Known hypersensitivity to any component of BMN 110
- Major surgery within 3 months before study entry or planned major surgery during the 24 week treatment period
- Pregnancy or breastfeeding at Screening or planning to become pregnant (self or partner) any time during study
- Use of any investigational product or medical device within 30 days before screening or requirement for any investigational agent before completion of all scheduled study assessments

Investigational Plan

Of 177 subjects randomized, 175 were allocated 1:1:1 to one of three treatment groups: (1) BMN 110 2.0 mg/week, (2) BMN 110 2.0 mg/kg/qow with placebo infusions on alternate weeks, or (3) placebo for 24 weeks. Randomization was stratified by 2 factors: screening 6MWT categories (≤ 200 meters and > 200 meters and age group (5-11, 12-18, and ≥ 19 years of age). Subjects, Investigators, and study site personnel were blinded to treatment assignment throughout the trial and until the final analysis was complete. A physical examination and endurance tests (6MWT and 3MSCT, in duplicate) were performed at Screening and/or baseline, Week 12, and Week 24. Urine samples for keratin sulfate and creatinine and blood samples for immunogenicity testing were collected at baseline, Weeks 2 and 4, and every 4 weeks thereafter.

Primary Efficacy Variable

The 6MWT was performed according to American Thoracic Society Guidelines[9]. Subjects were instructed to walk as far as possible in 6 minutes, with ambulatory aids permitted as long as their use was consistent throughout the trial. Heart rate and oxygen saturation were measured immediately before the start of each 6MWT, immediately after its completion, and 2 minutes after its completion. Two 6MWTs were performed at screening, Weeks 12 and 24, and within 1 week of early withdrawal from the trial. Two 6MWTs were conducted at each time point, with only one test to be performed on a given day. The average of the 2 measurements was used as the score for the visit week. The endurance tests were performed during the 5 days before infusion in the following order: 6MWT, 3MSCT, 6MWT, 3MSCT.

Secondary Efficacy variables

The 3MSCT[10] was performed unless clinically contraindicated. The test was performed over 3 minutes, with number of stairs climbed during that interval recorded as the result.

The same flight of stairs was used for each subject and time point at each site. Heart rate and oxygen saturation were measured immediately before the start of each 3MSCT, immediately following its completion, and 2 minutes after its completion. The 3MSCTs were performed at the same intervals as the 6MWTs, and the average of the 2 measurements was used as the score for the visit week.

Statistical methods

In MOR-004, the Week 24 change from Baseline in the 6MWT distance was the primary efficacy endpoint. The primary analysis of the primary endpoint was the analysis of covariance (ANCOVA) of the Week 24 change from baseline in the 6 MWT measurement using a model with treatment, age stratification (5-11, 12-18, ≥ 19 years), and Baseline 6MWT stratification (≤ 200 meters and > 200 meters) as factors.

Efficacy results

6MWT The sponsor reported the BMN 110 0.2.0 mg/kg/week dosing regimen as meeting the primary endpoint. There was a 23.7 meter mean improvement in 6MWT at Week 12 and a 36.5 meter improvement at Week 24, representing a 14.9% mean improvement over placebo. Administration of the every other week regimen did not significantly improve 6MWT compared to placebo. The estimated treatment effect at Week 24 for the weekly regimen compared with placebo was 22.5 meters and for the qow regimen 0.5 meters. Patients whose screening 6MWT distance tended toward the lower level of inclusion (≥ 30 meters) appeared to benefit from a greater treatment effect than those initially able to walk longer distances.

3MSCT The 2.0 mg/kg/week regimen showed minimal advantage over placebo in the three-minute stair climb test, and the qow regimen showed no advantage over placebo. The estimated treatment effect at Week 24, compared with placebo, was 1.1 stairs/min for the weekly dosage regimen, and -0.5 stairs/min for the qow regimen.

Urine KS Treatment with BMN 110 reduced urinary keratan sulfate in both treatment arms. The estimated treatment effect at Week 24, compared with placebo, was -40.7% for the 2.0 mg/kg/week regimen, and -30.2% for the qow regimen.

MPS HAQ The MPS HAQ results numerically improved in the Caregiver Assistance and Mobility domains, but not in the Self-Care domain. To understand the potential influence of treatment on wheelchair and walking aid use, *post hoc* analyses were performed to more closely examine results from this objective individual question, which is not included in the Mobility Domain Score. In MOR-004, no wheelchair was required at baseline by 35 subjects (59.3%) in the placebo group, 23 subjects (39.0%) in the BMN 110 qow group, and 27 subjects in the BMN 110 weekly group. The number of subjects using a wheelchair at Week 24 increased by 5 (8.8%), and 0 (0.0%) in both BMN 110 groups.

Anthropometry Although an exploratory objective, the treatment effect of BMN 110 on anthropometric measurements was evaluated at Week 24. Anthropometric measurements were taken at Baseline and Week 24 and included standing height, length, sitting height,

and weight. The growth rate on study was compared to the growth rate prior to study entry for subjects who had growth measurements within 2 years prior to enrollment. For each subject, the pre-study growth rate was estimated as follows:

[Standing height *z*-score measured at Baseline-standing height *z*-score closest to, but not greater than, 2 years prior to study entry]/ Time (in years) between measurements

The sponsor reports the treatment effect at Week 24 for both BMN 110 dosing regimens in MOR-004 as trending toward improvement in normalized standing height and growth rate *z*-scores in males ≤18 years and females ≤ 15 years. Long-term follow up is ongoing in the extension study MOR-005.

Safety

Treatment with BMN 110 for 24 weeks appeared to be generally well tolerated with the majority of adverse events being consistent with those expected to be seen in an untreated MPS IV A population. In Trial MOR-004 there were no adverse events leading to permanent study discontinuation and no deaths. One patient in the BMN 110 0.2 mg/kg qow had an SAE of anaphylactic reaction but this patient subsequently tolerated BMN 110 infusions without recurrence of symptoms. The most common adverse events related to BMN 110 were infusion-related.

MOR-005 extension study

This is an ongoing study designed in two parts to evaluate the two dosage regimens of BMN 110 in subjects who have completed MOR-004. Of the 175 patients enrolled in MOR-004, 173 were enrolled in MOR-005. The study is planned to continue until patients have received 240 weeks of treatment. Part 1, completed on November 30, 2012 was a randomized double-blind study that continued until the primary analysis of MOR-004 was completed. In Part 1, subjects initially randomized to BMN 110 in MOR-004 remained on their assigned dose regimen. Patients initially randomized to placebo were re-randomized (1:1) to one of the two BMN 110 dose regimens (2.0 mg/kg/weekly or 2.0 mg/kg/qow). After analysis of the primary efficacy and safety results in MOR-004 and Drug Monitoring Committee recommendation, the dose for Part 2 of MOR-005 was determined as 2.0 mg/kg/weekly and all subjects were transitioned to this dosing regimen.

In Part 1, every 12 weeks each subject completed safety and efficacy assessments using urine keratan sulfate normalized to creatinine, physical examination, clinical laboratory assessments, immunogenicity tests, and pregnancy testing when appropriate. The 6MWT and 3MSCT were performed at Week 12 and Week 24 and then at 24 week intervals thereafter. Every 24 weeks, anthropometry, respiratory function testing, and audiometry were performed, the MPS Health Assessment Questionnaire was completed and blood samples for evaluating exploratory biomarkers were collected.

In Part 2, every 24 weeks each subject completes safety and efficacy assessments as above in Part 1, although respiratory function testing, electrocardiography, echocardiography, the 6MWT and 3MSCT are performed every 48 weeks. Every 72

weeks subjects have radiographs of the cervical and lumbar spine and, and for subjects ≤ 20 years of age, of the lower extremities.

Discussion

The primary trial in BLA 125460, MOR-004 has provided what appears to be beneficial yet inconclusive endurance data supporting enzyme replacement therapy with BMN 110. A prespecified minimal clinically important difference (MCID) for key efficacy endpoints was not defined prior to unblinding MOR-004. To analyze these endpoints with a responder analysis, the sponsor implemented a literature review and a Delphi consensus panel for *post hoc* review. The literature review focused on identifying publications which described an MCID for the endpoints of interest in diseases which have similar physical impairments (eg, chronic obstructive pulmonary disease, osteoarthritis, juvenile idiopathic arthritis, idiopathic pulmonary fibrosis, etc.) and use similar outcome measures, including the six-minute walk test (6MWT), stair climbing tests, or pulmonary function testing. Studies that investigated percent change from baseline yielded consistent results in the 10-14% range for 6MWT. There were no reports investigating an MCID for the three-minute stair climbing test (3MSCT). There also was limited evidence for the MCID for pulmonary function tests despite their role as primary outcomes in most respiratory disease trials.

The 6MWT is a well-standardized, simple, safe, and inexpensive test, and has been the basis for registration of several pharmaceutical products. It is a self-paced submaximal endurance test. The walk test is well established as a useful measure of functional status in patients with cardiorespiratory disease[1], and has also been used as a measure of exercise capacity in pediatric populations affected by chronic diseases such as cystic fibrosis[2], arthritis[3], and congenital heart disease[4]. The 6MWT has been used to assess adults with multiple sclerosis and after cerebrovascular accident. The 6 minute walk distance for normal 12 year olds has been measured at over 600 meters[5]. The 6MWT measures the integrated function of at least 3 separate organ systems that are affected by MPS IV A: the respiratory, cardiovascular, and musculoskeletal systems.

Ambulation is problematic for MPS IV A patients. On instrumented gait analysis, children with MPS IV have significant differences in the temporospatial characteristics, kinetics, and kinematics in their baseline gait pattern compared with the normal population[12]. Patients walk slowly with short stride lengths, even when normalized for their short stature. Montano et al. reported that only 10% of patients were able to ambulate more than 800 meters, almost 20% needed crutches, and 33% needed wheelchairs[11].

The walk test has been used to assess the effectiveness of enzyme replacement therapy in MPS I[6], MPS II[7], and MPS VI[8]. In the MPS I double blind, placebo-controlled phase III enzyme replacement therapy reported by Wraith et al[6]., 6 months of treatment with laronidase increased the 6MWT by 38 meters (P=0.025). In MPS II, patients treated with idursulfase weekly or every other week experienced a 37 meter improvement in 6MWT

by Week 53. In MPS VI, 6 months of treatment with galsulfase produced a difference of 92 ± 40 meters in a 12 minute walk test favoring galsulfase over placebo.

A consensus panel of recognized MPS experts were queried using the Delphi method and agreed that most of the typical MPS IV A symptoms can be directly or indirectly evaluated using the endpoints of 6MWT, 3MSCT, and maximal voluntary ventilation (MVV), and that these would be the most relevant endpoints for inclusion in the outcome analysis in the Phase III trial of BMN 110. Consensus recommendations for the responder definition threshold expressed as the percent change improvement over baseline after 24 weeks of treatment were as follows:

- A 15% change for the 6MWT to be applied to all subjects meeting the baseline walking criterion (30-325 meters).
- A 20% change for the 3MSCT to be applied to all subjects, not applicable to subjects unable to climb stairs at baseline.
- A 20% change for MVV, with a strong opinion that this threshold may not apply to subjects with a baseline MVV less than 10 L/min.

The Delphi panel wished to see greater changes in 6MWT in subjects with shorter baseline walking distances (30-100 meters) than for those subjects with longer or longest baseline 6MWT distances and also proposed alternative more detailed responder definitions for *post hoc* analysis:

- 20% for baseline 6MWT $\geq$ 30 meters but < 100 meters
- 15% for baseline 6MWT $\geq$ 100 meters but < 200 meters
- 10% for baseline 6MWT $\geq$ 200 meters but $\leq$ 325 meters

In Trial MOR-004, the treatment effect based on the percent change in distance walked from baseline to Week 24 was 14.9%, consistent with the recommendation for a 15% improvement in walking distance (Table 2):

Table 2 MOR-004 Trial Results for ITT Population

	Placebo N = 59	**2 mg/kg QW n = 58**	**Treatment Effect (QW-Placebo)**
Distance Walked, Change from Baseline to Week 24, meters			
Mean (SD) Median Min, Max 95% CI	14 (51) 10 -99, 221 0.6, 26	36 (58) 20 -58, 229 23, 49	22.5 m, CI95 (4.0, 40.9) P=0.0174
Percent Change from Baseline to Week 24 (%)			
Mean (SD) Median 25th , 75th Percentile Min , Max 95% CI Limit	8.7 (28.83) 3.8 -9.8 , 22.6 -45.6 , 105.4 -0.0 , 17.5	23.8 (44.43) 10.3 -0.4 , 33.5 -38.7 , 257.9 15.0 , 32.6	14.9% CI95 (2.7, 27.2) P=0.017 (post hoc analysis)

There was a 14.9% improvement from Baseline to Week 24 in all subjects, closely approximating the Delphi panel's recommendation for meaningful treatment effect. However, the proportion of patients meeting the responder definition in the weekly group compared to the placebo group reflected a small overall treatment effect and questionable clinical benefit (Table 3):

Table 3 MOR-004 Proportion of Patients meeting the Delphi Group Responder Definition (*post hoc)*

	Placebo N=59	**BMN 110 0.02 mg/kg/wk N=58**
6MWT Overall % change	18/59 (31%)	26/57 (46%)
Subgroup 6MWT % change	20/59 (34%)	27/57 (47%)
3MSCT 20% change	15/59 (25%)	26/57 (46%)

When the improvement in 6MWT was evaluated for each subject individually overall, only 46% of BMN-treated patients vs. 31% of placebo-treated patients met the responder definition of 15% improvement. While some patients exhibited significant improvement, many did not. When subgroups defined by baseline 6MWT were evaluated by the predetermined improvement criteria, only 47% of BMN-treated patients met the responder definition.

In Trial MOR-004, increase in 6MWT with 24 weeks of BMN 110 therapy was 36.5 meters in the weekly treatment group, and 14 meters in the placebo group, for a treatment effect of 22.5 meters. Despite meeting the agreed-upon 15% improvement in endpoint, the responder analysis calls the clinical meaningfulness of this improvement into question.

Statistical significance was not reached in the 3MSCT. The estimated treatment effect in the ITT population at Week 24, compared to placebo, was 1.1 stairs/minute for the BMN 110 2.0 mg/kg/week regimen, and -0.5 stairs/minute for the qow regimen.

The phenotypic spectrum of MPS IV A is reflected in the eligibility criteria for MOR-004, which appear designed to include enrollment of subjects who are broadly representative of the overall patient population. However, this necessary conflation of phenotypes in MOR-004 complicates its analysis. Efficacy of BMN 110 treatment for MPS IV A may be further investigated by post marketing requirements to be more clearly defined and implemented in extension study MOR-005. While relevant Baseline disease characteristics appear to be stratified appropriately in MOR-004, clinical outcome measures should continue to be clearly related to disease severity and age at initiation of treatment in MOR-005.

Questions posed to DBRUP by DGIEP

Question 1. For the musculoskeletal deformities and symptoms of the MPS IV A population described above, please advise us on additional clinical outcome measures that may better demonstrate change in musculoskeletal function with treatment. For these additional clinical outcome measures, explain reliable methods used for measurement in clinical practice or research, the frequency of measurements, and over what interval one would expect to see change.

DBRUP response

Possible alternative endpoints/ postmarketing requirements

Sequential pelvic and lower extremity x-rays

Common presenting symptoms of MPS IV A include progressive genu valgum, metaphyseal flaring, and hip instability[11]. Progressive hip subluxation, genu valgum, and ankle valgus were observed in all (23) untreated MPS IV A patients evaluated at one center[13]. Effective enzyme replacement therapy should stabilize or perhaps improve such findings. While there is no accepted radiographic index for assessing the severity of MPS IV A, scoring methods have been developed for other disorders, such as osteoarthritis, rheumatoid arthritis, and rickets.

Standard pelvic radiographs may be used for measuring well-accepted indices of hip instability. These include the neck-shaft angle, lateral center edge angle of Wiberg, percent femoral head coverage, and acetabular index[14].

Sequential full-length lower extremity anteroposterior and lateral weight-bearing radiographs may be evaluated for standard lower limb deformity measurements. These include anatomic tibiofemoral angle, mechanical lateral distal femoral angle, medial proximal tibial angle, anatomic posterior distal femoral angle, anatomic posterior proximal tibial angle, lateral distal tibial angle, and anatomic anterior distal tibial angle[15, 16].

In Trial MOR-004, in subjects ≤ 20 years old, radiographs of the lower extremity were obtained at Baseline and Week 24 for 36, 36, and 42 subjects in the placebo, BMN 110 qow, and BMN 110 weekly groups respectively. While no changes in bone length were reported, no other data were reported in the MOR-004 Clinical Study Report. The sponsor plans to obtain follow up radiographs in the extension phase protocol, MOR-005, at (b) (4) weeks following the Week 24 observation in MOR-004 and every (b) (4) weeks for the duration of MOR-005 (240 weeks). As the natural history of lower extre ty deformity and hip instability in MPS IV A is unknown, semi-annual assessment appears reasonable to monitor treatment effect until growth cessation.

We believe that these images in the extension study MOR-005 should be obtained every 24 weeks instead of every 72 weeks to better document treatment effect, recognizing that assay sensitivity is proportional to the age of treatment initiation and phenotypic severity.

Obtaining sequential pelvic and lower extremity radiographs may prove to be a safe, reproducible, and cost-effective means of indirectly monitoring disease severity of MPS IV A and response to treatment. However, the accuracy and value of such analysis must be tempered by a lack of a control group and the unclear natural history of hip instability and lower extremity deformity across the spectrum of MPS IV A phenotypes.

Serial spinal radiographs

In the Morquio A Clinical Assessment Program[19], 85% of subjects had kyphoscoliosis as a presenting finding. This may be due to defective chondrocyte production of Collagen II,

the major structural protein that provides cartilage with strength and resilience, and a major component of the nucleus pulposus of the normal intervertebral disc. While the natural history of spinal deformity in MPS IV A is unclear and may not be characterized in all cases by progression[25], effective therapy should improve the properties of abnormal cartilage that exacerbate dwarfism and spinal deformity.

In Trial MOR-004, radiographs of the cervical and lumbar spine were obtained at Baseline for 53, 49, and 53 subjects in the placebo, BMN 110 qow, and BMN 110 weekly groups respectively. Also, flexion-extension cervical spine radiographs were obtained to determine if the planned endurance testing was contraindicated by instability. No data are provided in the MOR-004 Clinical Study Report. (b) (4) No specific mention of the intervals between subsequent follow up radiographs is made.

To assess treatment effect on spinal deformity, sequential standing anteroposterior and lateral radiographs of the thoracolumbar spine on single images should be obtained semiannually until skeletal maturity. Recumbent images may be obtained if patients are unable to stand. Saggital and coronal plane alignment should be measured using a goniometer and standard Cobb technique, with angles measured from the intersection of perpendiculars from the endplates of the superior and inferior vertebrae in the coronal and saggital planes. Structural scoliosis may be distinguished from compensatory curvatures by side-bending X-rays; postural kyphosis may be determined by prone-lying lateral images taken over a chest bolster.

In extension trial MOR-005, subjects have radiographs of the cervical and lumbar spine taken at (b) (4) week intervals. We believe standing thoracolumbar x-rays should be obtained at 24 week intervals to better document treatment effect.

Radiographs of the thoracolumbar spine in MPS IV A patients can be expected to demonstrate overall spinal deformity and individual vertebral body platyspondyly. Stabilization or correction of these findings may prove to be a means of assessing disease progression and treatment effect. However, assay sensitivity for spine x-rays in MPS IV A patients would appear to be very sensitive to age at diagnosis and at initiation of treatment. Also, the lack of a control group and the unclear natural history of overall spinal and individual vertebral body deformity in MPS IV A would temper such an analysis.

Sequential spinal MRI

No international standards for evaluating MRI findings in mucopolysaccharidoses currently exist, although regular and systematic evaluation of these patients using a reproducible scoring system could be very useful for evaluating and monitoring these patients and providing a better insight into the natural history of these disorders[17]. Some efforts have been made to develop MRI scoring systems for spinal cord disease[23]. A study presented at the 2008 Annual Symposium of the Society of Inborn Errors of Metabolism used a scoring system for spinal cord involvement[18]. This scoring system

includes cervical MRI findings of odontoid hypoplasia, peri-odontoid soft tissue mass, posterior longitudinal ligament (PLL) hypertrophy, subluxation of the atlantoaxial joint and thoracolumbar findings of beaked vertebrae, concavity of the posterior vertebral wall, kyphosis and spinal cord involvement (Table 4). There is currently no consensus on the usefulness of such a scoring system.

Table 4. Scoring severity of spinal magnetic resonance imaging findings

Cervical MRI	
Odontoid hypoplasia	Not present Present
Peri-odontoid soft tissue mass	Not present Present
PLL hypertrophy	Not present Present
Intraspinal compromise	1=Subarachnoid space only 2=Spinal cord compression, no signal change 3=Spinal cord compression with T2 hyperintense area
Thoracolumbar MRI	
Beaked vertebra	Not present Present
Posterior vertebral body wall concavity	Not present Present
Kyphosis	Not present Present
Intraspinal compromise	1=Spinal canal narrowing without involvement of roots or conus 2=Spinal canal narrowing with stretching of roots due to bone changes

While improvement in scoring severity may indicate treatment benefit, the relative utility of MRI evaluation of patients with MPS IV A is compromised in some cases by the necessity of a general anesthetic and neurophysiologic monitoring. As the natural history of spinal cord compression is unknown across the spectrum of MPS IV A phenotypes,, there is no scientific basis for a recommendation for frequency of MRI evaluation for all cases. The incidence of cord compression in severe MPS IV A is such that some investigators have recommended prophylactic elective posterior cervical fusion in all cases[24]. While the sponsor may consider implementing MRI analysis as a parameter of treatment effect, this will likely be of limited utility given the lack of pre-randomization baseline images, the lack of a control group during the extension study, and lack of general acceptance of any scoring system for disease severity.

Biopsy confirmation of cartilage biodistribution and benefit of BMN 110

The sponsor has demonstrated the *in vitro* uptake and corrective effect on accumulated keratan sulfate and abnormal collagen gene expression profiles in human MPS IV A chondrocytes cultured with rhGALNS[22]. The sponsor could perform a similar analysis in a subset of subjects with cell cultures from paired biopsies before and after treatment with BMN 110. However, such analysis would be entirely exploratory.

Use of alternative outcomes instruments

There are no validated outcomes instruments for MPS IV A. Outcomes instruments for assessment of pediatric and adolescent musculoskeletal health developed by the American Academy of Orthopaedic Surgeons in collaboration with the Council of Musculoskeletal Societies and the Council of Spine Societies have been tested for validity and reliability. Input for these instruments was provided by the Pediatric Orthopaedic Society of North America, the American Academy of Pediatrics, and Shriner's Hospitals (Appendix). These instruments may provide further insight into the status of MPS IV A patients when analyzed in conjunction with the MPS HAQ.

However, certain aspects of these instruments do not appear applicable to the MPS IV A population. The Sports and Physical Function Domain and Core Scale inquire about degree of athletic participation. The Happiness Domain and Core Scale measures self-perception and body image.

Continuation of anthropometric measurements
This is reported as ongoing in extension study MOR-005. Growth rate and standing height *z*-scores should be monitored until skeletal maturity and reported.

> **Question 2** Provide your perspective of the relevance of the six-minute walk test and three-minute stair climb test to the MPS IV A population.

DBRUP response
Disorders such as MPS IV A can reduce endurance capacity by compromising central hemodynamics, peripheral circulation, ventilatory efficiency, muscle strength, and joint function. The six-minute walk and three-minute stair climb tests appear to measure the integrated function of at least 3 separate organ systems that are affected by MPS IV A: the respiratory, cardiovascular, and musculoskeletal systems. However, DBRUP does not have the expertise to comment on whether these tests will sufficiently assess functional capacity and treatment effect in MPS IV A patients. A rheumatology consult may provide more insight into this issue.

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Appendix

http://www.aaos.org/research/outcomes/outcomes_peds.asp

Instrument	**Organizations Collaborating in Development**
POSNA/PODCI Pediatric Instruments	
Pediatric Adolescent (self and parental report)	• American Academy of Orthopaedic Surgeons® • Pediatric Orthopaedic Society of North America • American Academy of Pediatrics • Shriner's Hospitals

AAOS - Outcomes-AAOS.url

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/s/

JOHN T STINSON
09/13/2013

THERESA E KEHOE
09/13/2013

HYLTON V JOFFE
09/13/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125460 **Applicant: Biomarin** **Stamp Date: March 29, 2013**

Drug Name: Vimizim (BMN-110) NDA/BLA Type: BLA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS narrative = Clinical Summary of Safety (module 2.7.4); ISS tables, listings, and datasets are in module 5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	No ISE. One pivotal study.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1) BLA
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? • MOR-002 Phase 1 /2 Dose escalation trial evaluated 0.1, 1, and 2 mg/kg/week dosing regimens; N=20 • MOR-004 Phase 3 pivotal trial and MOR-005 extension trial evaluated 2 mg/kg weekly and every other week dosing regimen; N = 176 Location in submission: Module 5.3.5	X			
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Mor-004 RCT, placebo-controlled for 26 weeks 1:1:1 2mg/kg weekly, 2 mg/kg qow, placebo N = 176 Indication: MPS VIA	X			Sponsor presents a single pivotal study with multiple supportive studies
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	U.S. population represented.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Biologics currently not known to have arrythmogenic potential.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Being a rare disease, the Division agreed that a minimum of 50 patients who have completed 1 year of treatment with BMN 110 at the proposed dose of 2.0 mg/kg/week was adequate. Separate addendum to ISS in module 5.3.5.3
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Immunogenicity and hypersensitivity reactions. Sponsor provided a separate "Integrated Immunogenicity Report."
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			No Deaths. Sixteen patients with SAEs; 3 considered drug-related
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			**See attachment at the end of this document.**
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan Designation
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	U.S. population represented.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse	X			CRFs for patients in ongoing trials

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Tamara Johnson, MD, MS — April 25, 2013
Reviewing Medical Officer — Date

Jessica J. Lee, MD — April 25, 2013
Clinical Team Leader — Date

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Attachment:

Data requested by the Division during pre-BLA meeting

Requested item	Provided?	Comment
Safety: At least 50 patients who have exposed to drug for 1 year	Y	
Efficacy: Recommend conducting a longer (1-2 year long) placebo-controlled trial to evaluate the efficacy of BMN110 because it appears from your extension study that there could be continued improvement in 3 MSCT and 6 minute walk test (6MWT) that may be attributable to a treatment effect. Without a controlled trial, we cannot be sure that the trends toward improvement in the 3MSCT and 6MWT seen in the extension study are related to a BMN 110 treatment effect.	N	Highly Recommended; now assessment of treatment effect becomes a review issue
Abbreviated CSRs in Module 5 for the two ongoing extension studies (MOR-100 and MOR-005) and two ongoing ancillary phase 2 studies (MOR-007 and MOR-008).	Y	
Data for studies MOR-007 and MOR-008 should be provided in electronic format upon submission; interested in exploring safety and efficacy data for MOR-008	Y	
Provide all immunogenicity data	Y	
Submit electronic copies of all CRFs at the time of submission even for patients in ongoing trials.	Y	
Provide graphs in which you have delta uKS (from baseline to 24 weeks) on the y-axis and the delta in the various clinical measures (6MWT, 3MSCT, and maximum voluntary ventilation) at 24 weeks	Y	
Provide a histogram of change from Baseline to Week 24 in the 6 MWT (m) in the ITT population with categorical intervals of improvements (and decrements) on the X-axis, as opposed to a cumulative grouping on the X-axis (groupings were for ≥ to a certain level of improvement). We request you do the same for the 3 MSCT and the MVV.	Y	Figure 14.2.1.10: 6-Minute Walk Test , Figure 14.2.2.10: 3-MSC, Figure 14.2.4.8: Maximum Voluntary Ventilation
Nonclinical: carcinogenicity assessment	Y	
Clinical Pharmacology Summary in Module 1.11.4	Y	
Your data suggested that a higher dose than what you tested in MOR-004 may have better efficacy. Provide justifications for the selection of 2 mg/kg.	Y	2.7.3 SCE 2.7.2 SCPS
OSI: Site level data	Y	

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/s/

TAMARA N JOHNSON
05/15/2013

JESSICA J LEE
05/16/2013