Food and Drug Administration
Center for Drug Evaluation and Research

The Endocrinologic and Metabolic Drugs Advisory Committee Meeting

November 19, 2013

Briefing Document

Vimizim (elosulfase alfa)

For patients with Mucopolysaccharidosis Type IVA
(MPS IVA; Morquio A syndrome)

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought elosulfase alfa to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Executive Summary

1.1 Statement of Purpose

The purpose of the Advisory Committee meeting is to obtain advice regarding whether the totality of clinical information supports approval of elosulfase alfa for the treatment of patients with Mucopolysaccharidosis Type IVA (MPS IVA; Morquio A syndrome). Specifically, the Agency is seeking advice on the appropriateness of the six-minute walk test (6MWT) to adequately evaluate treatment benefit in patients with MPS IVA, and whether the magnitude of change observed in 6MWT and other measures represents a clinically meaningful benefit in this patient population.

1.2 Background

On March 29, 2013, BioMarin Pharmaceuticals Inc. (the Applicant) submitted a biologics license application (BLA) to support U.S. marketing approval of Vimizim (elosulfase alfa) for the treatment of MPS IVA. MPS IVA is a rare, autosomal recessive lysosomal storage disease caused by a deficiency in N-acetylgalactosamine-6-sulfate sulfatase (GALNS). Missing or insufficient enzyme activity results in impaired catabolism of glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate (C6S). The accumulation of GAGs in multiple organs and tissues leads to significant morbidities and multisystemic clinical impairments. Elosulfase alfa is intended to provide the exogenous enzyme GALNS that will be taken up into the lysosomes and subsequently increase the catabolism of the GAGs.

Patients with MPS IVA present with progressive skeletal dysplasia (including joint deformities/contractures, short stature, atlantoaxial instability, and spinal cord compression), valvular heart disease, reduced respiratory function, hearing loss, cataracts, and corneal clouding. Unlike other mucopolysaccharidoses, patients with MPS IVA have normal intelligence. Musculoskeletal impairment and respiratory dysfunction have the greatest impact on these patients' lives. Death is most commonly due to airway obstruction and spinal cord compression. Currently, there is no approved therapy for MPS IVA.

The Applicant used the six-minute walk test (6MWT) to assess the treatment benefit in adult and pediatric patients with MPS IVA who are 5 years and older. The 6MWT was originally developed to measure the functional capacity and endurance in adult patients with moderate to severe heart or lung diseases. Since then, its use has been expanded to both adult and pediatric patients with various chronic conditions, such as cystic fibrosis, Duchenne muscular dystrophy, and obesity. In addition, the 6MWT has been used to support U.S. marketing approval of multiple products, including those intended to treat rare inborn errors of metabolism, such as alglucosidase alfa to treat Pompe disease, laronidase to treat MPS I, idursulfase to treat MPS II and galsulfase to treat

MPS VI*. For most of these diseases, an improvement in respiratory function (i.e., forced vital capacity) was also used to support approval.

It is important to note that clinical manifestations and prognoses can vary between different diseases. While patients with Pompe disease and MPS I, II and VI tend to have more extensive cardiopulmonary involvement that affects their endurance, patients with MPS IVA experience difficulty ambulating largely due to progressive skeletal dysplasia, such as joint deformities and contractures.

Currently, there is no widely accepted method of assessing treatment benefit in patients with MPS IVA, and it is not clear whether limited ambulation due to skeletal dysplasia is best assessed by 6MWT. No prior therapies have been approved to treat this patient population using an established endpoint.

1.3 Clinical Summary

1.3.1 Efficacy

The Applicant submitted one adequate and well-controlled phase 3 clinical trial (MOR-004) to support the effectiveness of elosulfase alfa for treatment of patients with MPS IVA. MOR-004 was a 24-week, randomized, double-blind, placebo-controlled trial in 176 patients with MPS IVA that evaluated two dosing regimens of elosulfase alfa, 2 mg/kg/dose once weekly (2 mg/kg QW) and 2 mg/kg/dose once every other week (2 mg/kg QOW), compared with placebo. The proposed marketing dose of elosulfase alfa is 2 mg/kg QW.

The primary efficacy endpoint was defined as the change in distance walked in the six-minute walk test (6MWT) from baseline to Week 24. Although the Agency agreed that the 6MWT could be used as a primary efficacy measure, the Applicant was advised to analyze the primary endpoint using a responder analysis. A responder is defined as a score change in a measure, experienced by an individual patient over a predetermined time period, that has been demonstrated in the target population to represent treatment benefit. Due to the heterogeneity in disease presentations, the Applicant reported difficulty defining a responder that could be used as a primary endpoint. Therefore, the pre-specified primary endpoint remained as change in 6MWT from baseline to Week 24.

Patients in the elosulfase alfa 2 mg/kg QW treatment group demonstrated a statistically significant change in the 6MWT compared to placebo at Week 24, based on the pre-specified Analysis of Covariance (ANCOVA) model (mean difference of 22.5 meters; 95% CI [4.0, 40.9]; $p = 0.0174$), whereas patients in the elosulfase alfa 2 mg/kg QOW treatment group performed similarly to those in the placebo group (mean difference of 0.5 meters; 95% CI [-17.8, 18.9]; $p = 0.9542$). The numerical difference of 22.5 meters

* Approval of galsulfase to treat MPS VI was based on a 12-minute walk test.

between the elosulfase 2 mg/kg QW and placebo groups appears modest (an average city block is approximately 80 to 100 meters long). In this document, we present several exploratory analyses that were conducted to better assess the clinical meaningfulness of this result. The Advisory Committee will be asked to opine whether a 22.5-meter improvement in walking distance in MPS IVA patients would be a clinically meaningful improvement.

The secondary efficacy endpoint, the change in three-minute stair climb test (3MSCT), did not demonstrate a similar trend as the 6MWT. Neither the elosulfase alfa 2 mg/kg QW nor the elosulfase alfa 2 mg/kg QOW treatment group demonstrated a statistically significant change in the 3MSCT compared to placebo at Week 24. The elosulfase alfa 2 mg/kg QW treatment group demonstrated a greater difference from placebo on the 3MSCT, but the mean difference (based on the pre-specified ANCOVA model) in stair climb rate between these two treatment groups was only 1.1 stairs per minute.

After taking a closer look at the best performers on the 6MWT, we evaluated the mean change in 6MWT by baseline walking ability (6MWT ≤ 200 meters *vs*. > 200 meters at baseline) in an exploratory analysis. Patients who walked shorter distances at baseline (6MWT ≤ 200 meters) showed a greater improvement in walking ability than those who walked > 200 meters at baseline. Among patients who walked ≤ 200 meters at baseline, the mean change in 6MWT from baseline to Week 24 was 53 meters on elosulfase alfa 2 mg/kg QW treatment *vs*. 13 meters on placebo. Among patients who walked > 200 meters at baseline, the mean change in 6MWT from baseline to Week 24 was 25 meters on elosulfase alfa 2 mg/kg QW treatment *vs*. 14 meters on placebo. These exploratory results suggest that elosulfase alfa treatment might be more effective in patients with more severe disease at baseline.

Additional exploratory analyses are planned to assess the change from baseline in 6MWT by baseline measures of respiratory function (% predicted FVC, FEV_1, and MVV).

Based on long-term data collected from an extension study (MOR-005), patients who continued to receive elosulfase alfa 2 mg/kg QW for another 48 weeks (for a total of 72-week exposure) did not demonstrate additional improvement on 6MWT over what was demonstrated during the 24-week controlled trial (MOR-004). However, their walking ability seems to have stabilized and overall remained better than prior to initiating therapy. It is important to interpret these data with caution since there was no placebo comparator group in the extension trial. Interestingly, a group of patients who received placebo during MOR-004 and subsequently randomized to receive elosulfase alfa 2 mg/kg QW in MOR-005 did not experience any improvement in 6MWT with initiation of therapy. However, their walking ability remained stable throughout the extension trial. It is not clear whether enzyme replacement therapies are able to reverse preexisting skeletal damage. If skeletal dysplasia is already severe when initiating therapy, it is possible that treatment with enzyme replacement therapy may only allow prevention of further progression.

In summary, treatment with elosulfase alfa 2 mg/kg once weekly resulted in a modest improvement in the 6MWT in MPS IVA patients. There was no similar improvement in the 3MSCT. Based on exploratory subgroup analysis, the improvement in 6MWT was more pronounced among patients who walked shorter distances at baseline. This observation suggests that elosulfase alfa may be more efficacious in a subgroup of patients who have more limitations in mobility. Long-term uncontrolled data indicated no further improvement on the 6MWT with continued therapy, but showed stabilization in walking ability over time.

1.3.2 Safety

A total of 235 patients were included in the safety population, and consisted of patients who were enrolled in MOR-004 as well as five other supportive trials. Fifty of 235 patients were treated with elosulfase alfa 2 mg/kg QW (proposed marketing dose) for at least 52 weeks.

Anaphylaxis and hypersensitivity reactions are the major safety concerns for all enzyme replacement therapies, including elosulfase alfa. All patients in MOR-004 received premedication with antihistamines with or without antipyretics. Eighteen of 235 (7.7%) patients treated with elosulfase alfa experienced anaphylaxis, which was defined using the 2006 National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) Criteria for Anaphylaxis. Signs and symptoms of anaphylaxis 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. Hypersensitivity reactions were reported in 64 (27%) patients. Frequent symptoms of hypersensitivity reactions included angioedema, urticaria, peripheral edema, facial edema, wheezing, flushing, cough, dyspnea, and rash.

There were no deaths. 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%).

As with all therapeutic proteins, there is a potential for the development of immunogenicity. All patients treated with elosulfase alfa 2 mg/kg once weekly in MOR-004 developed anti-drug antibodies by Week 4. By Week 16, approximately 96% of the weekly-treated patients developed neutralizing antibodies capable of inhibiting the drug from binding the mannose-6-phosphate receptor. Binding to this receptor is required for elosulfase alfa to be taken into cells where it is active. Antibody titers were sustained or increased for the duration of elosulfase alfa treatment, including the extension phase. Since the majority of patients developed neutralizing antibodies and neutralizing

antibody titers were not assessed, there are currently inadequate data to assess the relationship between antibody development and therapeutic response or occurrence of anaphylaxis or other hypersensitivity reactions.

In summary, approximately 8% of patients treated with elosulfase alfa experienced anaphylaxis. The adverse reactions were similar to those seen in other enzyme replacement therapies. However, most patients developed anti-drug antibodies and neutralizing antibodies. Further studies may be needed to better understand the role of antibody development on long-term efficacy and safety.

1.4 Advisory Committee Topics for Discussion

The FDA requests that the Advisory Committee consider the following discussion topics during review of this (and the Applicant's) briefing document. These topics are intended to frame the Committee's deliberations at the meeting, and include:

1. Discuss whether a change in 6MWT from baseline to Week 24 adequately evaluates treatment benefit in patients with MPS IVA. Discuss other potential measures of treatment benefit that could be assessed in MPS IVA patients.

2. Discuss whether the totality of clinical data supports the effectiveness of elosulfase alfa for treatment of MPS IVA.

    a. Consider whether the magnitude of treatment difference observed in the 6MWT and 3MSCT represent a clinically meaningful benefit in this patient population.

    b. Discuss whether an exploratory analysis based on baseline walking ability provides clinical support that elosulfase alfa treatment might be more effective in patients with more limitations in mobility.

    c. Discuss additional exploratory analyses that could further support that clinical trial results of 6MWT reflect clinical benefit in patients with MPS IVA.

3. Discuss your assessment of the available neutralizing antibody data to evaluate the impact of these antibodies on safety and efficacy of elosulfase alfa for treatment of MPS IVA. If appropriate, discuss potential studies that could address this concern.

2 Background Information

2.1 Clinical Description of MPS IVA

Mucopolysaccharidosis IV Type A (MPS IVA), or Morquio syndrome Type A, is a rare, lysosomal storage disease caused by mutations in the gene encoding the enzyme, N-acetylgalactosamine-6-sulfate sulfatase (GALNS). Without functional GALNS enzyme, the glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate (C6S) are not degraded and accumulate within the cell lysosome. This pervasive and progressive accumulation of GAGs in multiple organs and tissues leads to significant morbidities and multisystemic clinical impairments.

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 usually present with 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 genetic analysis.

Disease presentation and progression vary by patient. Patients with more progressive (severe) disease typically present with skeletal dysplasia prior to one year of age and die in the 2nd or 3rd decade of life. Patients with attenuated (mild) disease are diagnosed in adulthood with less bone deformity and have been reported to survive into the seventh decade of life.[1,2]

The clinical features of MPS IVA include progressive skeletal dysplasia (including joint deformities/contractures, short stature, spinal cord compression), reduced pulmonary function, valvular heart disease, hearing loss, cataracts, and corneal clouding.[2] Unlike other mucopolysaccharidoses, patients with MPS IVA have normal intelligence. Musculoskeletal and respiratory dysfunctions have the greatest impact on these patients' lives. Patients describe most bothersome symptoms as fatigue, decreased endurance, joint stiffness and pain.[3] Up to one-third of MPS IVA patients who walk require a walking aid to ambulate.[4] 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 most commonly due to respiratory failure, cardiac

1 Hendriksz CJ, Harmartz P, Beck M, et al. Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA. *Mol Genet Metab* 2013;110:54-64.
2 Montaño AM, Tomatsu S, Gottesman GS, et al. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. *J Inherit. Metab Dis* 2007;30:165–174.
3 Based on a teleconference held on May 21, 2013, where MPS IVA patients and their caretakers shared with FDA reviewers clinical signs and symptoms that are most troublesome to MPS IVA patients.
4 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.

disease, or central nervous system complications (i.e. atlantoaxial subluxation, spinal cord compression).[2]

There is currently no approved effective treatment for MPS IVA. 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. Data collected from the International Morquio A Registry questionnaire suggest that 56% of patients undergo one or more surgeries, with the most frequent surgeries being cervical spinal cord decompression/fusion (51%), ear tube placement (33%), osteotomy (26%), and hip reconstruction and replacement (25%).[2] Hematopoietic stem cell transplantation has been attempted in some patients with MPS IVA, but a clear benefit has not been established.[5]

Elosulfase alfa is intended to provide the exogenous enzyme GALNS that will be taken up into the lysosomes and subsequently increase the catabolism of the GAGs, specifically KS and C6S. This mechanism of action is hypothesized to reverse the disease process in MPS IVA.

2.2 Evaluating Treatment Benefit in MPS IVA

MPS IVA patients commonly present with progressive skeletal dysplasia (including joint deformities/contractures, short stature, spinal cord compression), restrictive and obstructive pulmonary disease, and valvular heart disease. The Applicant used the 6MWT to assess the treatment benefit in adult and pediatric patients with MPS IVA who are 5 years and older. The 6MWT was originally developed to measure the submaximal level of functional capacity in adult patients with moderate to severe heart or lung diseases (e.g., congestive heart failure, pulmonary hypertension, chronic obstructive pulmonary disease), as it has been shown to be a predictor of morbidity and mortality in these patients.[6,7] Since its inception, it has also been used to assess functional outcome in other patient populations, such as cystic fibrosis,[8] Duchenne muscular dystrophy,[9] and obesity.[10] Further, the 6MWT has been used to support U.S. marketing approval of a number of products, including those intended to treat rare inborn errors of metabolism, such as alglucosidase alfa to treat Pompe disease, laronidase to treat MPS

5 Tomatsu S, Montaño AM, Oikawa H, et al. Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment. *Curr Pharm Biotechnol* 2011;12:931-45.
6 Shah MR, Hasselblad V, Gheorghiade M, 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;88:987-93.
7 Miyamoto S, Nagaya N, Satoh T, 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;161:487-92.
8 Gulmans VA, van Veldhoven NH, de Meer K, et al. The six-minute walking test in children with cystic fibrosis: reliability and validity. *Pediatr Pulmonol* 1996;22:85-9.
9 McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. *Muscle Nerve* 2010;41:500-10.
10 Elloumi M, Makni E, Ounis OB, et al. Six-minute walking test and the assessment of cardiorespiratory responses during weight-loss programmes in obese children. *Physiother Res Int* 2011;16:32-42.

I, idursulfase to treat MPS II and galsulfase to treat MPS VI.* However, clinical manifestations and prognoses vary between different diseases. For example, patients with Pompe disease and MPS I, II and VI tend to have more extensive cardiopulmonary involvement that affect their endurance, but patients with MPS IVA experience difficulty ambulating largely due to skeletal dysplasia, such as joint deformities and contractures. It is not clear whether limited ambulation due to skeletal dysplasia is best measured by the 6MWT.

Currently, there is no widely accepted method of assessing treatment benefit in patients with MPS IVA, and no prior therapies have been approved to treat this patient population using an established endpoint. Since the 6MWT seems to capture the function of at least three organ systems affected in MPS IVA (i.e., musculoskeletal, respiratory, cardiovascular), the Agency believes that 6MWT might be an acceptable instrument to measure treatment benefit in this patient population. In the upcoming EMDAC meeting, the Agency seeks advice from the Committee on the appropriateness of the 6MWT to assess treatment benefit in this patient population, and other potential measures of short- and long-term treatment benefit that could be used in future clinical trials involving MPS IVA patients.

6-Minute Walk Test (6MWT)

The 6MWT measures the distance that a person can walk quickly in six minutes. The walking course should be a straight, hard and flat surface, measuring 30 meters (100 ft) in length with clearly defined turnaround points.[11] The walker may go at his own pace, resting as needed, within the prescribed testing time. Normal 6-minute walk test distances in healthy adults range from 500 to 580 meters, with men walking slightly longer distance than women.[12] In a modified 6MWT using a measuring wheel for motivation, healthy children aged 3 to 11 years walked from 492 to 667 meters. Boys walked longer distance than girls, and the distance walked increased with age and height.[13] Another study also reported that the 6MWT is correlated with age, height, and weight in children and adolescents.[14]

A prospective longitudinal study (supported by the Applicant) conducted in 316 MPS IVA patients 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).[4] In general, the mean distance walked on the 6MWT decreased with increasing age. Even at a young age, the impact of disease on walking ability was already evident. Table 1 compares the mean 6MWT by age group for healthy subjects,

* Approval of galsulfase to treat MPS VI was based on a 12-minute walk test.

11 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.

12 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998;158:1384–7.

13 Geiger R, Strasak, A, Treml B, et al. Six minute walk test in children and adolescents. *J Pediatr* 2007;150:395-9.

14 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.

MPS IVA patients described in a longitudinal study, and MPS IVA patients who participated in MOR-004.

Table 1: Mean 6MWT 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.
Source: FDA Clinical reviewer's table.

Although the 6MWT has been used widely to assess clinical outcome, it also has limitations. There is a wide range of variability in how the test is administered despite availability of guidelines. In addition, the test is effort-dependent, which could be particularly problematic in pediatric patients whose performance is often influenced by their developmental stage, understanding of the instructions and willingness to cooperate. The 6MWT results have been shown to vary by the type of chronic pediatric disease (i.e. cerebral palsy, cystic fibrosis, Duchenne muscular dystrophy, congenital heart disease, obesity, spina bifida), and therefore, should be interpreted with caution.[15] Experts have recommended using additional outcome measures to help interpret the clinical meaningfulness of the 6MWT results in each chronic disease population.

2.3 Product Information

Elosulfase alfa is a recombinant human N–acetylgalactosamine-6-sulfatase produced in a Chinese hamster ovary cell line. Elosulfase alfa is an enzyme that participates in the lysosomal degradation of glycosaminoglycans (GAGs), such as keratan sulfate (KS) and chondroitin-6-sulfate (C6S). The cellular uptake of enzyme into lysosomes is mediated by binding of mannose-6-phosphate-terminated oligosaccharide chains of elosulfase alfa to cation-independent mannose-6-phosphate receptors. Inside the lysosome, the enzyme cleaves the sulfate groups from the KS and C6S molecules, preventing their accumulation in cells and disruption of organ function.

15 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;93:529–41.

Elosulfase alfa is available as a sterile, nonpyrogenic solution that must be diluted with 0.9% normal saline solution prior to administration by intravenous infusion. The proposed marketing dose of elosulfase alfa is 2 mg/kg/dose given intravenously (IV) once weekly.

2.4 Relevant Regulatory History

There were a series of formal communications and meetings between the Applicant and the Division of Gastroenterology and Inborn Errors Products (DGIEP) during product development. Regulatory history relevant to the Advisory Committee discussion is summarized below:

- On December 3, 2010, the Applicant submitted their proposed phase 3 trial (MOR-004) for review under a Special Protocol Assessment (SPA). During review of the SPA protocol, The Division agreed that 6MWT could be used as a primary endpoint. However, the Division did not agree with the Applicant's proposed null hypothesis testing because the results could lead to a statistically significant difference that is not clinically meaningful. The Division advised the Applicant to revise the primary analysis plan to include an alternative hypothesis, or 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 an MCID in the MPS IVA population. A No Agreement letter was issued on January 20, 2011, and the Applicant chose not to pursue the SPA any further.

- During a pre-BLA meeting on December 11, 2012, **t**he Division expressed concerns about the short-term nature of the phase 3 efficacy data (i.e., 24 weeks) and highly recommended that a longer placebo-controlled trial (i.e., 1-2 year in duration) be conducted to evaluate the durability of efficacy.

The Applicant is seeking marketing authorization in Europe concurrently with this BLA review.

3 Sources of Clinical Data in BLA 125460

The clinical efficacy and safety of elosulfase alfa have been primarily evaluated in one trial: a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of elosulfase alfa 2 mg/kg/dose once weekly (2 mg/kg QW) and 2 mg/kg/dose once every other week (2 mg/kg QOW) in patients with MPS IVA (MOR-004), which serves as the single adequate and well-controlled trial in this clinical development program.

In the BLA submission, the Applicant also included supportive data from the completed phase 1/2 trial (MOR-002), two ongoing long-term extension trials (MOR-005 [extension of MOR-004] and MOR-100 [extension of MOR-002]), and two ongoing ancillary phase 2 trials (MOR-007 [evaluation in < 5 year olds] and MOR-008 [evaluation of a higher dose, 4 mg/kg QW]). Since these trials were not conducted to support efficacy for the proposed indication, MOR-004 was the primary focus of this BLA review. However, the Division also reviewed available long-term clinical data from an ongoing extension trial that followed MOR-004 (i.e., MOR-005) to assess the durability of response. At our request, the Applicant submitted additional efficacy data from MOR-005 through Week 72 during this review cycle.

The safety dataset included a total of 235 patients who were enrolled in MOR-004, as well as supportive trials. MOR-004 and MOR-005 are summarized in Table 2.

Table 2: Description of the Placebo-Controlled Trial (MOR-004) and the Open-Label Extension Trial (MOR-005)

Trial	Primary Objective	Trial Design	Dosing Regimen	Number of Patients	Patient Population	Duration
MOR-004	To evaluate the ability of elosulfase alfa 2 mg/kg QW and 2 mg/kg QOW, 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	Elosulfase alfa 2 mg/kg IV QW *or* Elosulfase alfa 2 mg/kg IV QOW *or* Placebo	177 randomized 176 dosed	MPS IVA patients 5 years and older who are able to walk 30-325 meters on the 6MWT	24 weeks
MOR-005	To evaluate the long-term safety and efficacy of elosulfase alfa administration at 2 mg/kg QW or 2 mg/kg QOW in patients with MPS IVA.	Phase 3 extension, multinational, multicenter, (double-blind until completion of MOR-004, followed by open-label phase)	Double-blind phase: Elosulfase alfa 2 mg/kg IV QW *or* Elosulfase alfa 2 mg/kg IV QOW Open-label phase: Elosulfase alfa 2 mg/kg IV QW (dose determined based on the final primary efficacy and safety analyses from MOR-004)	173 enrolled	MPS IVA patients who completed MOR-004	Up to 240 weeks

Source: Summarized from the Applicant's Listing of Clinical Studies, Module 5.2

4 Clinical Trial Description of MOR-004

4.1 Trial Design

MOR-004 was a phase 3, multinational (17 countries), multicenter (31 clinical sites), randomized, double-blind, placebo-controlled, parallel group trial in patients with MPS IVA that evaluated two dosing regimens of elosulfase alfa, 2 mg/kg/dose once weekly (2 mg/kg QW) and 2 mg/kg/dose once every other week (2 mg/kg QOW), compared with placebo. The Applicant selected the 2 mg/kg QW dosing regimen based on results from the phase 1/2 trial. The additional dosing regimen of 2 mg/kg QOW was added to determine whether patients could derive similar benefit with less frequent dosing and exposure.

Patients were randomized 1:1:1 to one of three treatment groups:

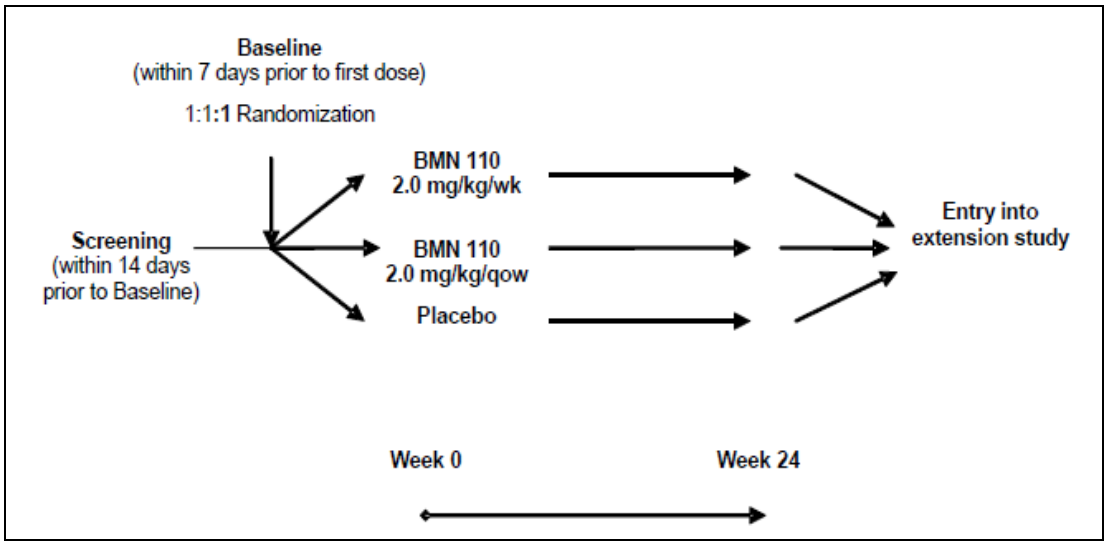
- elosulfase alfa 2 mg/kg/dose once weekly (2 mg/kg QW)
- elosulfase alfa 2 mg/kg/dose once every other week (2 mg/kg QOW), or
- placebo

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

All patients received pretreatment with antihistamines with or without antipyretics. Enrolled patients received assigned treatment for 24 weeks.

The study schema is shown in Figure 1.

Figure 1: MOR-004 Study Schema



Source: Applicant's study protocol for MOR-004, dated October 4, 2010, Figure 9.1.1.

It should be noted that all patients who were randomized into this trial were later given the opportunity to immediately roll over into a 240-week (5-year), uncontrolled extension trial (MOR-005) which assesses the long-term efficacy and safety of elosulfase alfa. This extension trial has two parts. In Part 1, all patients rolling over from MOR-004 who were dosed with elosulfase alfa stayed on their MOR-004 dose in a double-blinded fashion. Patients who received placebo in MOR-004 were re-randomized 1:1 to receive elosulfase alfa 2 mg/kg QW or 2 mg/kg QOW in a double-blinded fashion.
After completion of MOR-004 and final analysis of its primary efficacy and safety results, elosulfase alfa 2 mg/kg QW regimen was determined to be more effective and selected for administration in Part 2 of MOR-005. Part 1 of MOR-005 ended on November 30, 2012, and Part 2 is currently ongoing. All participating patients are currently receiving elosulfase alfa 2 mg/kg QW in an open-label fashion.

4.2 Objectives

The primary objective of MOR-004 was to evaluate the ability of elosulfase alfa 2 mg/kg/dose once weekly (2 mg/kg QW) and 2 mg/kg/dose once every other week (2 mg/kg QOW), compared with placebo, to enhance endurance in MPS VIA patients, as measured by an increase in number of meters walked in the 6-minute walk test (6MWT) from baseline to Week 24.

The secondary objectives of MOR-004 were:

- To evaluate the ability of elosulfase alfa 2 mg/kg QW and 2 mg/kg QOW, compared with placebo, to enhance endurance in MPS IVA patients, as measured by an increase in number of stairs climbed per minute in the 3-minute stair climb test (3MSCT) from baseline to Week 24.

- To evaluate the ability of elosulfase alfa 2 mg/kg QW and 2 mg/kg QOW, compared with placebo, to reduce urine keratan sulfate (uKS) levels in MPS IVA patients, as measured by a decrease in normalized uKS levels from baseline to Week 24.

There were multiple tertiary objectives, which included but were not limited to evaluation of PK parameters and respiratory function (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], maximum voluntary ventilation [MVV], forced inspiratory vital capacity [FIVC], and forced expiratory time [FET]).

In addition, MOR-004 evaluated the safety and tolerability of elosulfase alfa infusions over a 24-week period.

4.3 Study Population

Key Inclusion Criteria:

- At least 5 years of age with documented clinical diagnosis of MPS IVA based on clinical signs and symptoms and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA
- Must have an average screening 6MWT distance ≥ 30 and ≤ 325 meters

Key Exclusion Criteria:

- Previous hematopoietic stem cell transplant
- Previous treatment with elosulfase alfa
- Major surgery within 3 months prior to study entry or planned major surgery during the 24-week treatment period
- 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 study participation or safety as determined by the investigator

4.4 Endpoints

A clinically meaningful endpoint measures directly how a patient *feels*, *functions* or *survives*, and can provide evidence of efficacy for regulatory purposes. A clinically meaningful endpoint should capture signs and symptoms that patients and their caregivers consider most bothersome about the disease. Once a clinically meaningful endpoint has been identified, an *a priori* responder definition should be specified to aid in the interpretation of adequate and well-controlled trials. A responder is defined as a score change in a measure, experienced by an individual patient over a predetermined

time period, that has been demonstrated in the target population to represent treatment benefit.

The following primary and secondary endpoints were pre-specified by the Applicant; however, a responder definition was not pre-specified.

Primary endpoint: The change from baseline in 6MWT at Week 24.

Secondary endpoints:

- The change from baseline in 3MSCT at Week 24
- Percent change from baseline in normalized uKS levels at Week 24.

Tertiary endpoints included measurement of PK parameters, respiratory function, bone and cartilage metabolism biomarkers, anthropometric parameters (sitting and standing heights, weight), quality of life (MPS Health Assessment Questionnaire), hearing, cardiac valve function, and corneal clouding. However, all of these endpoints were exploratory in nature and not intended to support labeling claims.

Safety was assessed through adverse reactions, concomitant medications, surgical procedures, vital signs, physical examinations, clinical laboratory testing (clinical chemistry, hematology, and urinalysis), 12-lead electrocardiography, echocardiogram, and monitoring of anti-drug antibodies.

4.5 Visits and Procedures

The endurance assessments (6MWT and 3MSCT) were performed 5 days prior to elosulfase alfa infusion, or 2 days after infusion. These tests were performed in duplicate, on separate days, at screening and/or baseline, Week 12, and Week 24 (or within one week of the Early Termination Visit [ETV]). The two endurance tests were not performed on the same day. The tests were conducted in the following order:

6MWT #1 → 3MSCT #1 → 6MWT #2 → 3MSCT #2

Test results were averaged to determine final measurement.

The 6MWT measures the total number of meters walked in a 6-minute period. 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. Walking aids, such as braces, ankle-foot orthotics, splints, crutches, cane, or walker, were allowed but must be used consistently throughout the trial. If a walking aid was used during the screening visit, the same walking aid had to be used for future assessments.

The 3MSCT measures the average number of stairs climbed per minute over a 3-minute period (i.e., total number of stairs climbed in 3 minutes divided by 3). Patients

were instructed to walk up stairs with a handrail that could be used for support for three minutes, and the number of steps climbed was recorded.

Urine samples for uKS and creatinine and blood samples for immunogenicity testing were collected at baseline, Weeks 2 and 4, and every 4 weeks thereafter (or within one week of the ETV).

Detailed study visits and procedures are shown in Table 3.

Table 3: Schedule of Assessments in Trial MOR-004

			Weeks																								
Assessments and Events	**Screen**	**Base-line**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**ETV†**
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	X
Weight for purpose of drug preparation			X				X				X				X				X				X					
Physical examination	X														X												X	X
Audiometry examination		X																									X	
Anthropometry examination		X																									X	X
6-Minute walk test	XX														XX												XX	XX
3-Minute stair-climb test	XX														XX												XX	XX
Respiratory function		X																									X	X
ECG	X																										X	X
ECHO	X																										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	X
Clinical laboratory tests	X	X							X						X						X						X	X
Urine KS and creatinine		XX			X		X				X				X				X				X				X	X
PK assessment			X																						X			
Blood inflammatory biomarkers		X													X												X	X
Blood biochemical markers, bone and cartilage metabolism		X													X												X	X
Thyroid panel	X														X													
Urine pregnancy test	X	X													X												X	X
Immunogenicity tests		X			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	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	X

Assessments and Events	Screen	Base-line	Weeks																									
			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	ETV†
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		

† 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.

Source: Applicant's Clinical Study Report (CSR) for MOR-004, Table 8.5.1.1.

4.6 Statistical Analysis

The Applicant 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.

In order to control the overall study-wise Type I error rate (α), the step-down procedure was pre-specified by the Applicant to adjust for multiple comparisons in the analysis for the secondary endpoints, in the order previously presented in Section 4.4. The Hochberg method was nested within each step/endpoint testing when comparing each of the two doses to placebo. Hence, the step-down can be carried to the next step if both doses at the current endpoint/step are found to be statistically significant (i.e., *p*-value < 0.05) in comparison to placebo. If at least one dose is found to be not statistically significant (i.e., *p*-value ≥ 0.05) compared to placebo at the current endpoint/step, all hypothesis testing for subsequent endpoints would be deemed as exploratory.

Primary Endpoint Analysis

For the 6MWT, two assessments were conducted at each visit at Weeks 0, 12, and 24. The arithmetic mean of the two measurements (in meters) was used as the score for the visit week. The primary 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. The comparison was conducted in a pair-wise fashion (i.e., separately for each dose *vs*. placebo).

Secondary Endpoint Analysis

Similar to the 6MWT, two assessments were conducted at each visit at Weeks 0, 12, and 24 for the 3MSCT. The arithmetic mean of the two measurements was used as the score for the visit week. The primary analysis was an ANCOVA model of the change in 3MSCT 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 and baseline 3MSCT as a covariate.

Urine keratan sulfate (uKS) and urine creatinine (for normalization) were measured through quantitative laboratory analysis. The Applicant calculated normalized uKS concentration to creatinine using the following formula:

Normalized urine KS = urine KS / urine creatinine

The baseline values were calculated as the average of the two measurements collected during the baseline week. The analysis of the normalized uKS was an ANCOVA model of the Week 24 percentage change from baseline in the normalized uKS measurement with treatment groups, baseline 6MWT categories (≤200 meters and >200 meters) and age groups (5-11, 12-18, and ≥19 years old) as factors and baseline normalized uKS as a covariate. The treatment comparisons conducted were identical to those for the primary endpoint analysis.

5 Efficacy Review

5.1 Indication

The Applicant proposes the following indication:

"Vimizim is indicated for patients with Mucopolysaccharidosis Type IVA (MPS IVA; Morquio A syndrome)."

5.2 Demographics and Baseline Clinical Characteristics

The baseline demographic information of patients who participated in MOR-004 is described in Table 4.

Table 4: Baseline Patient Demographics (MOR-004)

	Placebo (n = 59)	Elosulfase alfa 2 mg/kg QOW (n = 59)	Elosulfase alfa 2 mg/kg QW (n = 58)
Age at Enrollment (years)			
Mean (SD)	15 (11)	15 (11)	13 (8)
Median	12	12	11
Min , Max	5 , 57	5 , 49	5 , 42
Age Group - n (%)			
5 - 11	30 (51%)	31 (53%)	32 (55%)
12 - 18	15 (25%)	16 (27%)	16 (28%)
≥ 19	14 (24%)	12 (20%)	10 (17%)
Gender – n (%)			
Female	32 (54%)	25 (42%)	32 (55%)
Male	27 (46%)	34 (58%)	26 (45%)
Race			
Asian	11 (19%)	15 (25%)	14 (24%)
Black or African American	0	2 (3%)	2 (3%)
White	44 (75%)	35 (59%)	36 (62%)
Other	4 (7%)	7 (12%)	6 (10%)

Source: Applicant's CSR for MOR-004, Table 10.2.1.

Overall, there were no significant imbalances in baseline characteristics between treatment groups. The age of patients ranged from 5 to 57 years, and approximately half of the trial population consisted of patients aged 5 to 11 years old. The majority of patients were White, and Asians represented approximately one-quarter of the trial population. The placebo treatment group had larger proportions of older patients (≥19 years) and Whites compared to the elosulfase alfa treatment groups.

Table 5 summarizes the baseline clinical characteristics of patients who participated in MOR-004. Patients receiving elosulfase alfa 2 mg/kg QW were slightly shorter in height than those receiving either placebo or elosulfase alfa 2 mg/kg QOW. Patients in the placebo group had a slightly better mean baseline 6MWT than either of the elosulfase alfa treatment groups (212 meters for the placebo group *vs*. 206 meters and 204 meters for the QOW group and QW group, respectively). Approximately 10% more patients used walking aids in the elosulfase alfa 2 mg/kg QOW treatment group (27%) than either the placebo (19%) or the elosulfase alfa 2 mg/kg QW (16%) treatment group. Other clinical characteristics, including medical history, baseline walk test categories (≤ 200 meters vs. > 200 meters), and baseline 3MSCT, were similar between treatment groups.

Table 5: Baseline Clinical Characteristics (MOR-004)

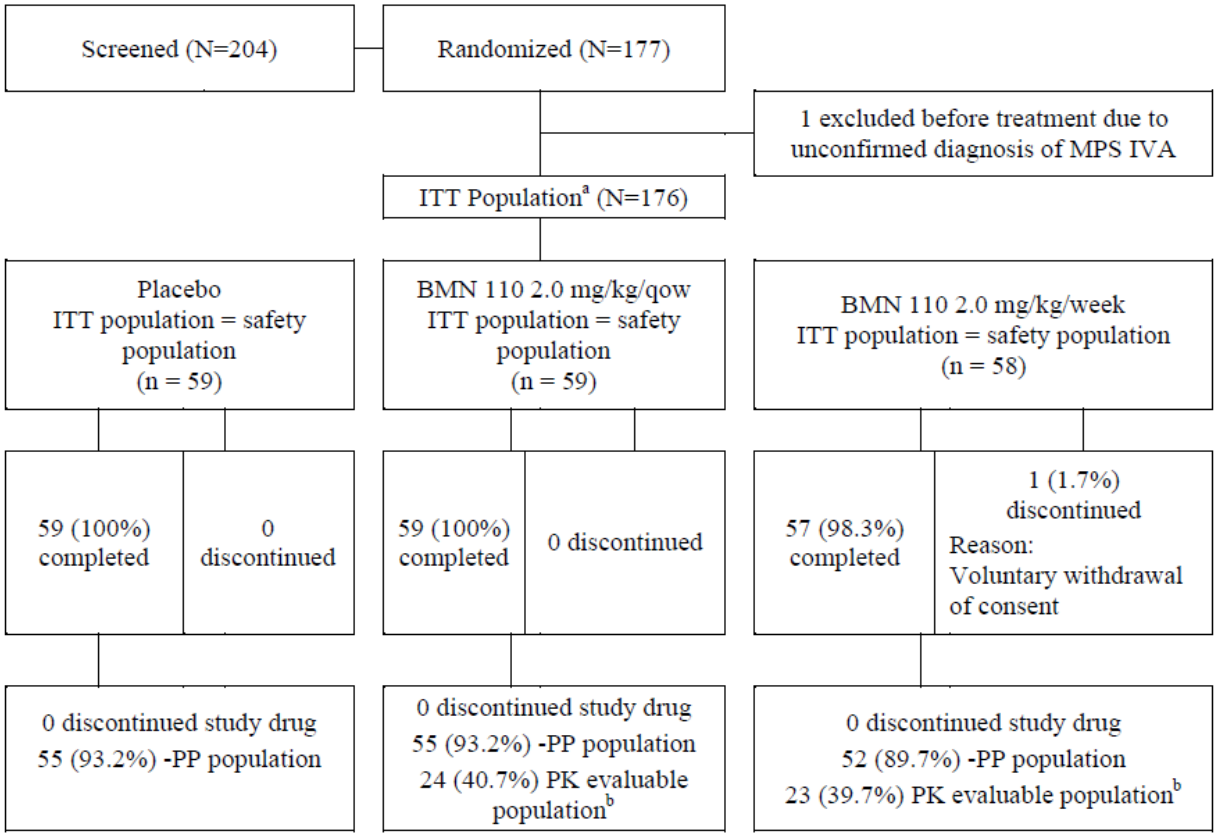
	Placebo (n = 59)	Elosulfase alfa 2 mg/kg QOW (n = 58)	Elosulfase afa 2 mg/kg QW (n = 58)
Height (cm):			
Mean (SD)	105 (17)	105 (16)	101 (13)
Median (Min, Max)	100 (86, 165)	100 (81, 147)	99 (83, 141)
<3rd percentile-for-age	92%	88%	97%
Medical History:			
• Musculoskeletal disorders	81%	86%	79%
• Surgical/med 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%)	9 (16%)
Walk Category			
• ≤200 meters	23 (39%)	24 (41%)	23 (40%)
• >200 meters	36 (61%)	35 (59%)	35 (60%)
6MWT (meters):			
Mean (SD)	212 (70)	206 (81)	204 (76)
Median (Min, Max)	229 (36, 312)	218 (47, 320)	217 (42, 322)
3MSCT (stairs/min):			
Mean (SD)	30.0 (14.1)	27.1 (15.8)	29.6 (16.4)
Median (Min, Max)	31 (0, 59)	26 (0, 67)	31 (0, 72)

† Patients used walkers, canes, or crutches.
Source: Adapted from the Applicant's CSR for MOR-004, Table 10.2.2 and 10.2.3.

5.3 Patient Disposition

Of the 204 patients screened to participate in the MOR-004 trial, 177 were randomized. The majority of patients (22 of 27) who failed screening had a screening 6MWT distance that exceeded the allowable maximum of 325 meters. Of the 177 patients who were randomized, one patient in the placebo group was not dosed because the diagnosis of MPS IVA was not confirmed. Of the 176 patients in the intent-to-treat (ITT) population, 59 patients were randomized to receive placebo, 59 patients to elosulfase alfa 2 mg/kg QOW, and 58 patients to elosulfase alfa 2 mg/kg QW. Of the 176 patients in the ITT population, 175 (99.4%) patients completed the trial and one (0.6%) patient in the QW group discontinued due to voluntary withdrawal of consent. Patient disposition is displayed in Figure 2.

Figure 2: Patient Disposition in MOR-004



[a] Intent-to-treat (ITT) population with no important protocol deviations.
[b] All placebo patients' PK parameters were not estimable. One patient who received elosulfase alfa 2 mg/kg QW had only one PK sample, a pre-dose sample at Week 0. Hence, this patient had no estimable PK parameters.
Source: Applicant's CSR for MOR-004, Figure 9.1.1.

Upon completion of MOR-004, patients rolled over to extension trial MOR-005. Table 6 summarizes the number of patients in each treatment group as they transitioned from MOR-004 to Part 1 of MOR-005.

Table 6: Patients per Treatment Group in MOR-004 and MOR-005 (Part 1)

MOR-004		MOR-005 (Part 1)	
Treatment Group	**n**	**Treatment Group**	**n**
Placebo	59	Placebo → QOW	29
		Placebo → QW	29
QOW	59	QOW → QOW	59
QW	58	QW → QW	56

5.4 Analysis of Primary Endpoint

5.4.1 Six-Minute Walk Test

The primary efficacy endpoint was the change in 6MWT from baseline to Week 24. Patients who received 2 mg/kg QW demonstrated a mean increase of 37 meters in distance walked, while those who received 2 mg/kg QOW and placebo had a mean increase of 15 meters and 14 meters, respectively. The mean difference using the ANCOVA model (see Section 4.6) between the elosulfase alfa 2 mg/kg QW group and placebo was 22.5 meters ($p < 0.05$). Based on the ANCOVA model, the mean difference between the elosulfase alfa 2 mg/kg QOW group and placebo was 0.5 meters ($p = 0.9542$). Therefore, a treatment effect was observed only in the elosulfase alfa 2 mg/kg QW treatment group. Table 7 summarizes the change in 6MWT from baseline to Week 24 for the elosulfase alfa 2 mg/kg QW treatment group (proposed indication) and placebo.

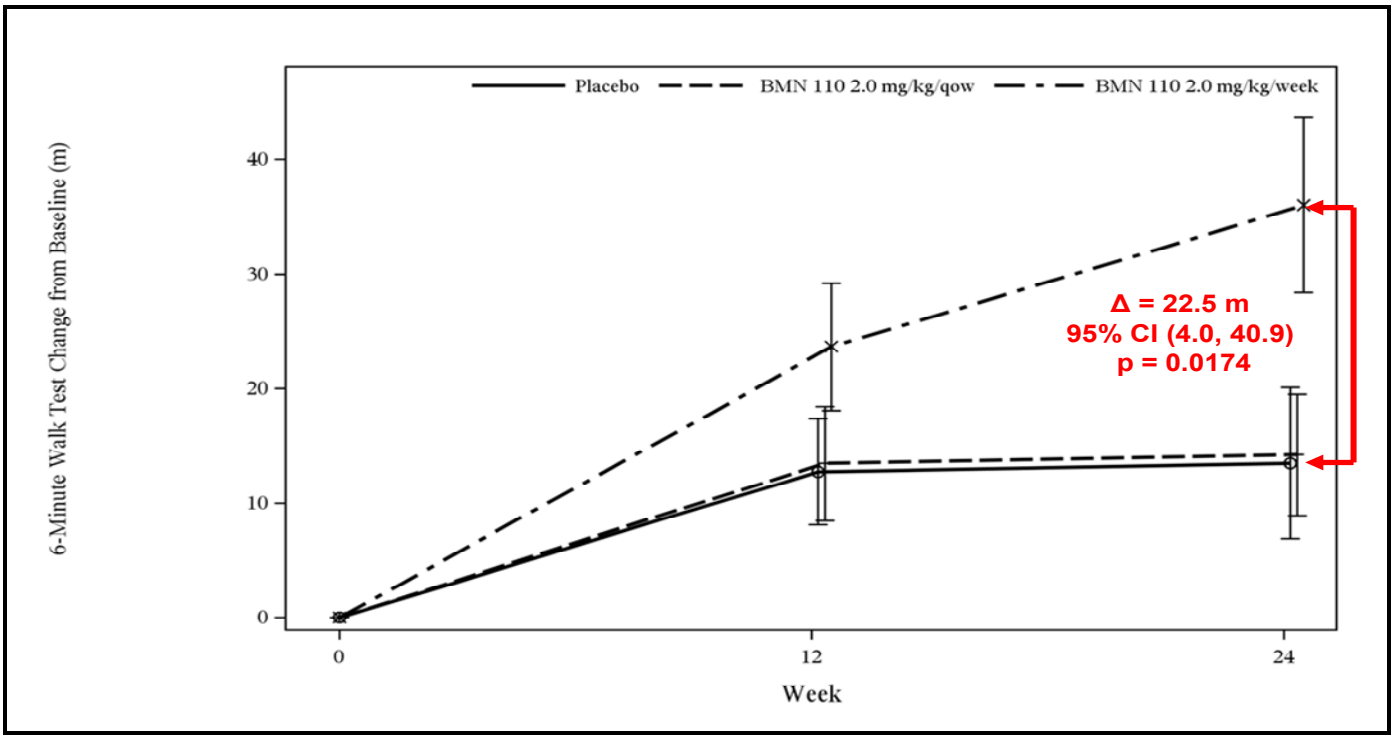
Table 7: Change in 6MWT from Baseline to Week 24 by Treatment Group (MOR-004)

	Placebo (n = 59)	**Elosulfase alfa 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 0.5, 27	37 (58) 20 -58, 229 23, 50	**22.5 meters** 95% CI (4.0, 40.9) $p = 0.0174$
Percent Change from Baseline to Week 24 (%)			
Mean (SD) Median 25th , 75th Percentile Min , Max 95% CI	8.7 (28.8) 3.8 -9.8, 22.6 -45.6, 105.4 (-0.1, 17.5)	23.9 (44.8) 10.0 -0.4, 33.5 -38.7, 257.9 (15.0, 32.9)	**14.9%** 95% CI (2.7, 27.2) $p = 0.017$ (exploratory analysis)

‡ Based on an ANCOVA model, adjusted for baseline age group and 6MWT category.
Source: Applicant's CSR for MOR-004, Table 10.4.2.1.9.

As shown in Figure 3, elosulfase 2 mg/kg QW dose was superior to placebo ($p = 0.0174$), while the elosulfase alfa 2 mg QOW dose was not.

Figure 3: Mean Change in 6MWT Distance (MOR-004)

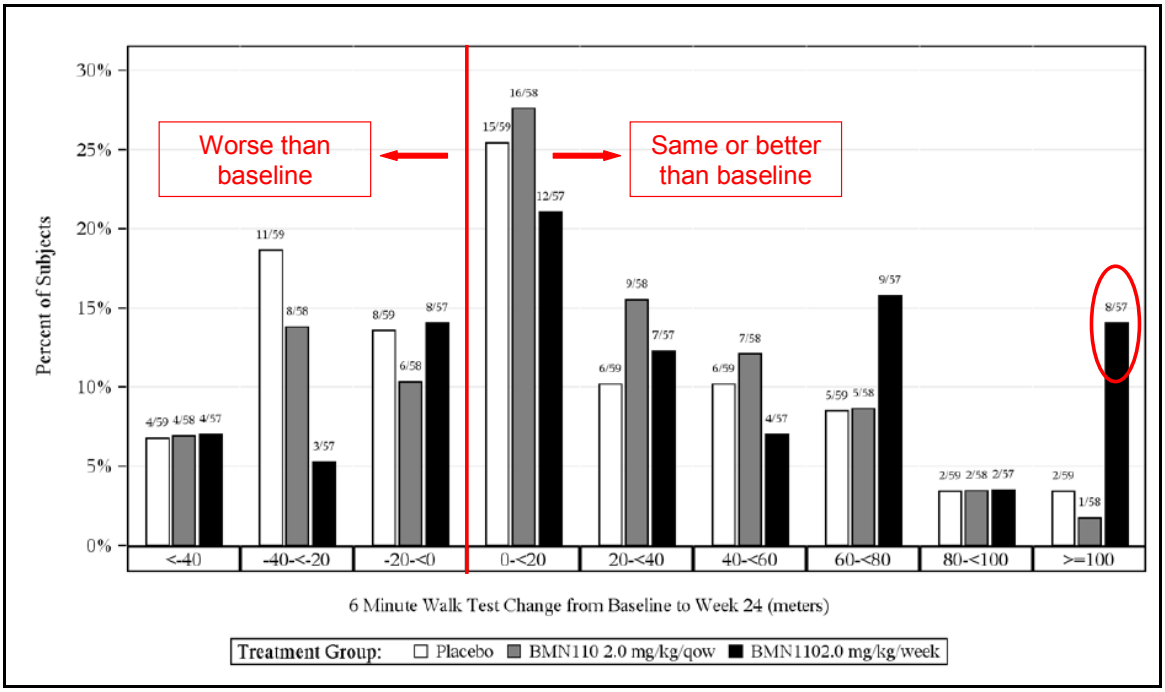


Source: Applicant's CSR for MOR-004, Figure 14.2.1.4 (annotations by FDA reviewer).

While the treatment difference between elosulfase alfa 2 mg/kg QW and placebo groups is statistically significant based on the pre-specified ANCOVA model, the observed magnitude of improvement is modest (mean improvement of 22.5 meters). To better understand the potential clinical meaningfulness of a 22.5-meter improvement in the MPS IVA patient population, we took a closer look at the best performers and also conducted several exploratory analyses.

Figure 4 illustrates the percentage of patients who achieved varying degree of improvements (or worsening) on the 6MWT from baseline to Week 24 by treatment group. While the distribution is similar between elosulfase alfa 2 mg/kg QOW and placebo groups, the elosulfase alfa 2 mg/kg QW group displayed two peaks of high performing patients: those who achieved an increase of 60 to ≤80 meters (n=9) and those who achieved ≥100 meters on the 6MWT (n=8).

Figure 4: Distribution of Change in 6MWT from Baseline to Week 24 by Treatment Group



Source: Applicant's CSR for MOR-004, Figure 14.2.1.10, p. 635 (annotations by FDA reviewer).

The eight patients in the elosulfase alfa 2 mg/kg QW group who achieved ≥100 meter change in 6MWT (circled in red in Figure 4) were evaluated further for characteristics that may have contributed to their high 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). There were no other discerning characteristics that could explain their high performance on the 6MWT, and their performance on the 6MWT did not translate to better performance on the 3MSCT (Table 8).

Table 8: 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

Source: FDA Clinical reviewer's table using the Applicant's dataset.

Exploratory analysis of their individual performance on the 6MWT suggested that patients who walk shorter distances at baseline may experience a greater improvement in the 6MWT on treatment. In other words, the 6MWT performance at Week 24 may be inversely related to 6MWT performance at baseline. This inverse relationship was further explored using the overall study population (see Section 5.4.2). In this small number of patients, the baseline 6MWT did not appear to correlate with either the 3MSCT at baseline or the change from baseline in the 3MSCT.

5.4.2 Exploratory Subgroup Analysis by Baseline 6MWT

When the change in 6MWT at Week 24 was evaluated by baseline 6MWT performance (≤ 200 meters *vs*. > 200 meters) in all patients, patients with worse baseline 6MWT (≤ 200 meters) showed a greater improvement in walking ability than those who could walk more than 200 meters at baseline (see Table 9). This observation is consistent with that displayed in the eight high performing patients described previously. It should be noted that a cut-off of 200 meters was used in this subgroup analysis, because the randomization was stratified by screening 6MWT categories of ≤ 200 meters and > 200 meters.

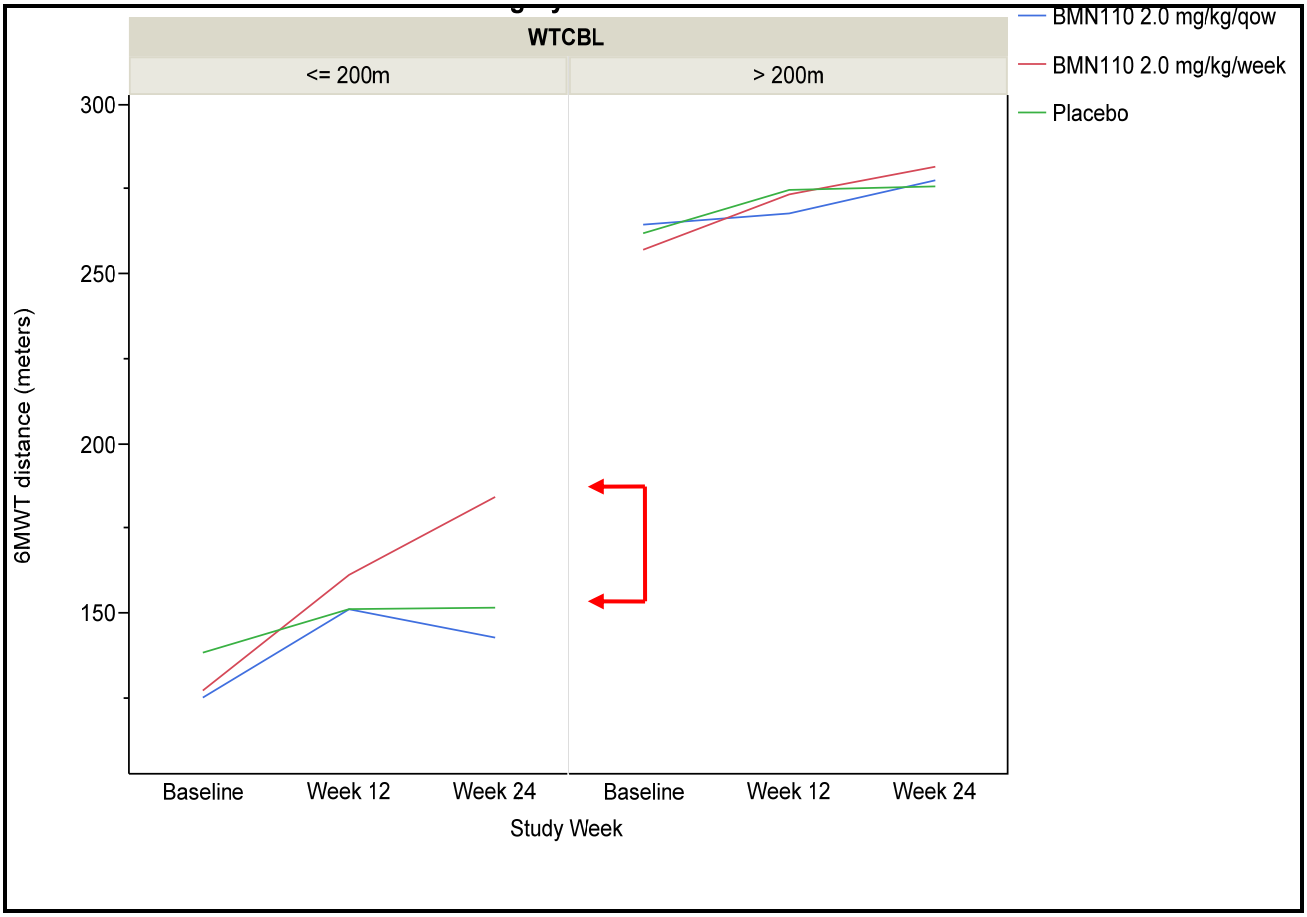
Table 9: Change in 6MWT from Baseline to Week 24 by Baseline 6MWT Performance (≤ 200 meters *vs*. > 200 meters)

Subgroup	Parameter	Placebo (n = 59)	2 mg/kg QW (n = 58)
Baseline 6MWD ≤200m	N Mean (SD) Median Min, Max 95% CI	23 13 (39) 11 -43, 95 (-8, 35)	23 53 (67) 35 -58, 229 (32, 75)
Baseline 6MWD >200m	N Mean (SD) Median Min, Max 95% CI	36 14 (57) 9 -99, 221 (-2, 30)	35 25 (49) 14 -51, 119 (8, 41)

Source: Applicant's CSR for MOR-004, Tables 14.2.1.26 and 14.2.1.28.

As shown in Figure 5, patients who walked ≤ 200 meters at baseline seem to have influenced the overall treatment effect of the elosulfase alfa 2 mg/kg QW group. The mean change in the 6MWT from baseline to Week 24 (using an ANCOVA model similar to that pre-specified for the primary analysis) was 40 meters greater than placebo among those in the ≤ 200-meter group, but only 11 meters greater than placebo in the > 200-meter group. However, it is important to note the exploratory nature of this analysis.

Figure 5: Exploratory Analysis - Distance Walked in 6 Minutes (meters) by Baseline 6MWT Performance (≤ 200 meters vs. > 200 meters) at Weeks 0, 12 and 24



Source: FDA Clinical reviewer's exploratory analysis using the Applicant's dataset.

Patients who walked ≤ 200 meters at baselines were evaluated for characteristics that may have contributed to their better performance on the 6MWT at Week 24 (see Table 10).

Table 10: Patients Characteristics by Baseline 6MWT Performance (≤ 200 meters *vs*. > 200 meters)

Parameters	Baseline 6MWT Performance	
	≤ 200 m	>200 m
n	71	106
Age		
Mean (SD)	17 (10)	13 (10)
Median (Range)	14 (5-47)	10 (5-57)
Gender		
Male	34 (48%)	54 (51%)
Race		
White	51 (72%)	64 (60%)
Asian	11 (15%)	30 (28%)
Black	2 (3%)	2 (2%)
Other	7 (10%)	10 (9%)
Height		
Mean (SD)	102 (15)	105 (15)
Median (Range)	99 (88-165)	101 (81-147)
<3rd percentile	62 (87%)	100 (94%)
Walking Aid Used	31 (44%)	5 (5%)
Medical History:		
-Musculoskeletal disorders	57 (80%)	86 (81%)
-Surgical/med procedures	58 (82%)	66 (62%)
-Eye disorders	48 (68%)	65 (61%)
-Cardiac disorders	36 (51%)	47 (44%)
-Respiratory disorders	38 (54%)	32 (30%)

Source: FDA Clinical reviewer's analysis using the Applicant's dataset.

Patients with worse baseline walking abilities (i.e., baseline 6MWT ≤ 200 meters) were slightly older. The use of a walking aid was more common among the ≤ 200-meter group, with 31 (44%) patients using a walker, cane or crutches. These 31 patients using walking aids were similarly distributed among the placebo and elosulfase alfa 2 mg/kg QW treatment groups. Only 5 of 106 patients in the > 200-meter group required a walking aid, and none of these 5 patients were assigned to the QW treatment group. Other demographic and clinical characteristics, such as gender, race, and height, were similar. In addition, these characteristics were balanced between the placebo and elosulfase alfa 2 mg/kg treatment groups.

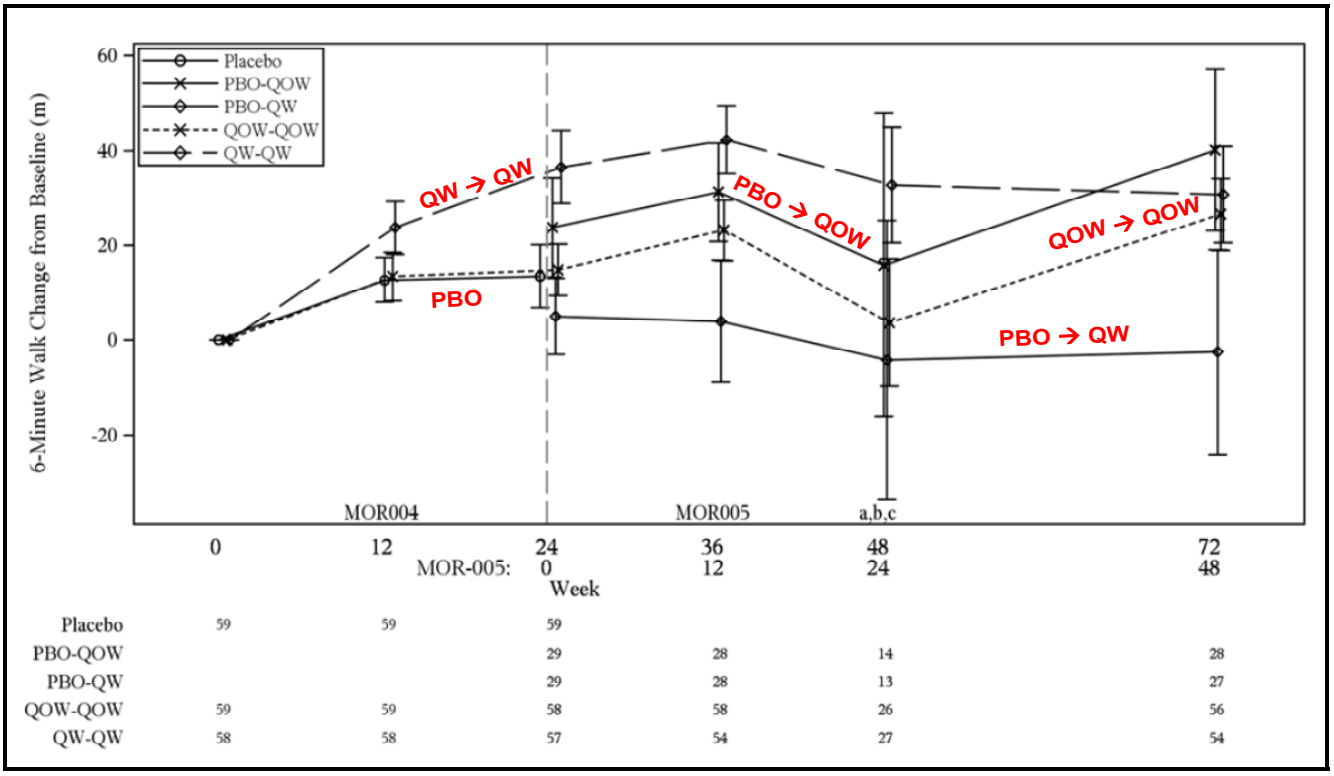
Additional exploratory analyses are planned to assess the change from baseline in 6MWT by baseline measures of respiratory function (% predicted FVC, FEV1, and MVV).

5.4.3 MOR-005 Extension Trial Data

As stated previously, all patients participating in MOR-004 were eligible to roll over into the long term efficacy and safety trial MOR-005. Of the 177 patients randomized into

the MOR-004 trial, 173 participated in the MOR-005 trial. Figure 6 displays the change in 6MWT from baseline through Week 72. This figure presents all 24 weeks of 6MWT data from the MOR-004 trial, along with the data from Part 1 of MOR-005 (double-blinded portion of the extension trial) and an additional 24 weeks of data from Part 2 of MOR-005 (open-label portion of the extension trial). MOR-005 is still ongoing at this time.

Figure 6: Mean Change in 6MWT from Baseline through Week 72 (MOR-004 Randomized Patients Rolling Over Into MOR-005)



Source: September 27, 2013 Information Request Information, Figure 14.2.1.1 (colored annotations by FDA reviewer).

Patients who remained on elosulfase alfa 2 mg/kg QW in the extension trial (QW→QW treatment group) achieved a peak increase in mean 6MWT of 42 meters after a total of 36 weeks of exposure. After 48 weeks of exposure, the mean change in 6MWT for the QW→QW treatment group decreased back to 33 meters, a similar level that was attained after 24 weeks of treatment in MOR-004 (i.e., mean change of 37 meters). However, Week 48 data should be interpreted with caution as there was a 50% reduction in sample size during this visit as only those patients who reached Week 48 while still in Part 1 of MOR-005 trial were included in the analysis. Part 1 continued only until completion of MOR-004 and final analysis of its efficacy and safety results. Since Part 2 does not have a Week 48 assessment, late enrollees of MOR-004 who transitioned directly from MOR-004 to Part 2 of MOR-005 do not have Week 48 assessment. By Week 72, the sample size increased close to that of MOR-005 at baseline.

Although there was no further improvement in 6MWT beyond 36 weeks of exposure, patients who continued to receive elosulfase alfa 2 mg/kg QW from baseline reasonably maintained their improvement of the 6MWT change from baseline scores through 72 weeks of exposure. The extension trial data must be interpreted with caution since there was no placebo control group for comparison. It is interesting to note that a group of patients who received placebo during MOR-004 and subsequently randomized to receive elosulfase alfa 2 mg/kg QW in MOR-005 (PBO → QW) did not experience any

improvement in 6MWT with initiation of therapy. Nevertheless, their walking ability remained stable throughout the extension trial.

5.5 Analysis of Secondary Endpoints

5.5.1 Three-Minute Stair Climb Test

The change in 3MSCT from baseline to Week 24 was a secondary endpoint in MOR-004. The baseline mean (SD) 3MSCT for all patients was 28.9 (15) stairs/min, ranging from 0 to 72 stairs/min (see Table 5 for baseline 3MSCT by treatment group). As shown in Table 11, patients in all treatment groups performed similarly on the 3MSCT. Based on the ANCOVA model described in Section 4.6, patients who received elosulfase alfa 2 mg/kg QW had a mean increase in 3MSCT of 1.1 stairs/min (95% CI [-2.1, 4.4]; p = 0.4935), compared with placebo. Patients who received elosulfase alfa 2 mg/kg QOW had a mean decrease in 3MSCT of 0.5 stairs/min (95% CI [-3.7, 2.8]; p = 0.7783), compared with placebo.

Table 11: Mean Change in 3MSCT (stairs/min) from Baseline to Week 24 by Treatment Group (MOR-004)

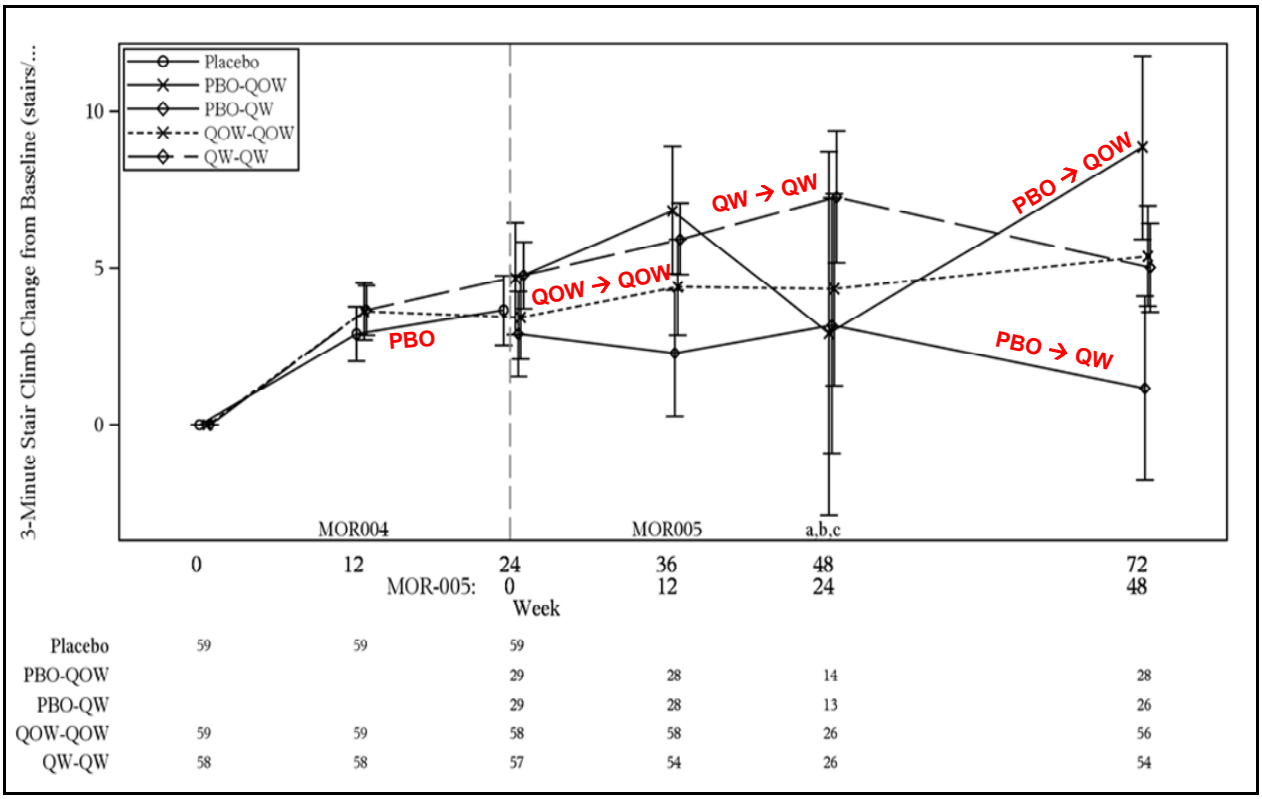
Parameter	Placebo (n = 59)	Elosulfase alfa 2 mg/kg QOW (n = 58)	Elosulfase alfa 2 mg/kg QW (n = 57)
Mean (SD)	3.6 (8.5)	3.4 (10.3)	4.8 (8.1)
Median	0.9	1.6	4.3
Min, Max	-13.0, 32.4	-19.3, 45.8	-12.4, 20.5
95% CI	(1.3, 6.0)	(1.1, 5.8)	(2.4, 7.1)

Source: Applicant's CSR for MOR-004, Table 14.2.2.8.

Patients who walked ≤ 200 meters on baseline 6MWT climbed fewer stairs (15-20 stairs/min on 3MSCT) than those who walked > 200 meters on baseline 6MWT (35-43 stairs/min on 3MSCT). However, there were no differences in the mean change from baseline in 3MSCT among treatment groups.

Figure 7 displays change in 3MSCT from baseline through Week 72.

Figure 7: Mean Change in 3MSCT from Baseline through Week 72 (MOR-004 Randomized Patients Rolling Over Into MOR-005)



Source: September 27, 2013 Information Request Information, Figure 14.2.2.1 (colored annotations by FDA reviewer).

Overall, the mean change in 3MSCT was small for both elosulfase alfa 2 mg/kg QW and elosulfase alfa 2 mg/kg QOW treatment groups. However, both groups reasonably maintained the change in 3MSCT from baseline through 72 weeks without worsening below baseline. It should be noted that at 48 weeks, only the data from approximately half of the enrolled patients are included. As stated previously, the extension trial data must be interpreted with caution since there was no placebo control group for comparison.

5.5.2 Urinary Keratan Sulfate Excretion Level

Based on the ANCOVA model described in Section 4.6, the normalized urinary keratan sulfate (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.

The normalized uKS reductions achieved statistical significance for both groups (exploratory in nature based on the Applicant's pre-specified multiplicity adjustment approach). 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 12 summarizes the mean percent change in uKS in elosulfase alfa-treated groups compared to placebo.

Table 12: Mean Percent Change in Normalized Urine Keratan Sulfate from Baseline to Week 24 by Treatment (MOR-004)

Parameter	Placebo (n = 59)	Elosulfase alfa 2 mg/kg QOW (n = 59)	Elosulfase alfa 2 mg/kg QW (n = 58)
Mean (SD)	-2.8 (8.0)	-12.2 (16.3)	-12.6 (9.6)
Median	-2.6	-10.0	-11.3
Min, Max	-22.0, 20.1	-107.6, 6.0	-43.9, 0.5
95% CI	(-6.0, 0.4)	(-15.4, -9.1)	(-15.8, -9.4)

Source: Applicant's CSR for MOR-004, Table 14.2.3.45.

In MOR-005, the uKS levels continued to decline through Week 72 in patients receiving elosulfase alfa 2 mg/kg QW. However, changes in uKS levels have not been shown to correlate with changes in 6MWT. As stated previously, all inferential statistics corresponding to this secondary endpoint are exploratory in nature.

5.6 Other Clinical Endpoints

The Applicant also evaluated multiple exploratory endpoints in MOR-004. The results of selected pulmonary function test and height measurements will be summarized briefly in this section.

Pulmonary Function Test

Table 13 summarizes the results of pulmonary function test, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and maximum voluntary ventilation (MVV). Based on exploratory analysis, elosulfase alfa-treated patients seem to trend toward a greater improvement in pulmonary function. It should be noted that these results do not reflect % predicted values (i.e., normalized for age, gender and height) and should be interpreted with caution.

Table 13: Pulmonary Function Test Results (MVV, FEV_1, and FVC) by Treatment Group (MOR-004)

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

Source: Applicant's CSR for MOR-004, Tables 10.4.1.3.1.1.1, 10.4.1.4.1.2.1 and 14.2.6.3.

Height Measurements

A longitudinal study (supported by the Applicant) revealed that the average height of MPS IVA patients is more than 5 standard deviations below that predicted by the CDC normal pediatric growth charts.[4] An exploratory analysis of sitting height, standing height and standing height z-scores showed modest numerical improvements in these measurements from baseline to Week 24 (Table 14).

Table 14: Change in Sitting Height and Standing Height by Treatment Group (MOR-004)

	Placebo N = 59	Elosulfase alfa 2 mg/kg QW n = 58	Treatment Effect (QW-Placebo)
Sitting height (cm) at baseline Mean (SD) Median (Min, Max)	 61.7 (17.3) 54.7 (46.0, 113.8)	 59.0 (14.9) 53.7 (26.5, 98.3)	
Change in sitting height (cm) from baseline to Wk 24 Mean (SD) Median (Min, Max)	 **2.9** (10.4) 0.5 (-2.6, 51.0)	 **3.0** (9.8) 0.6 (-8.5, 44.2)	Mean difference (SD): **0.1** (1.9)
Standing height (cm) at baseline Mean (SD) Median (Min, Max)	 105.5 (16.8) 100 (86.3, 165)	 101.3 (13.1) 98.8 (82.7, 141.4)	
Change in standing height (cm) from baseline to Wk 24 Mean (SD) Median (Min, Max)	 **0.9** (1.3) 0.5 (-2.2, 4.5)	 **1.2** (1.5) 1.2 (-3.3, 4.1)	Mean difference (SD): **0.3** (0.3)
Standing height z-score at baseline Mean (SD) Median (Min, Max)	 -6.0 (2.8) -5.6 (-11.4, -1.4)	 -6.4 (2.6) -6.5 (-11.0, -2.1)	
Change in standing height z-score from baseline to Wk 24 Mean (SD) Median (Min, Max)	 **-0.1** (0.3) -0.1 (-0.9, 0.7)	 **-0.0** (0.3) -0.1 (-0.6, 0.8)	Mean difference (SD): **0.1** (0.1)

Source: Applicant's CSR for MOR-004, Tables 14.2.10.2, 14.2.10.3, and 14.2.10.5.

Other exploratory clinical endpoints

Patients who received elosulfase alfa 2 mg/kg QW, compared with placebo, showed a small numerical improvement in the Caregiver Assistance and Mobility Domains, but not in the Self-Care Domain, in the Mucopolysaccharidosis Health Assessment Questionnaire (MPS HAQ). The MPS HAQ measures self-care (eating/drinking, dressing, bathing, grooming, toothbrushing, and toileting), mobility skills (dexterity, mobility, walking, stair clmbing, and gross motor skills), and the extent of caregiver assistance required to perform these activities.

Compared with placebo, there were no apparent treatment effects in hearing, echocardiogram, corneal clouding or lower extremity long bone length.

6 Clinical Pharmacology Summary

Following a single intravenous dose of elosulfase alfa 2 mg/kg at Week 0 in MOR-004, the elosulfase alfa concentrations rapidly declined with a mean half-life ($t_{1/2}$) of 7

minutes. After repeated dosing at Week 22, the mean clearance (CL) of elosulfase alfa decreased, while the maximal plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC_{0-t}) increased for both the elosulfase alfa 2 mg/kg QOW and elosulfase alfa 2 mg/kg QW groups. In addition, the mean $t_{1/2}$ increased to 19 and 35 minutes for the elosulfase alfa 2 mg/kg QOW and 2 mg/kg QW groups, respectively. These increases in exposure at Week 22 may be attributable to the formation of anti-elosulfase alfa neutralizing antibodies, which are capable of binding to and interfering with the cellular uptake of elosulfase alfa to the target tissues.

After administration of the first dose at Week 0, mean CL of elosulfase alfa appeared to be higher in pediatric patients (≤17 years old) compared with adults (>17 years old), 9.7 ± 3.1 mL/min/kg (n = 22) *vs*. 6.0 ± 1.8 mL/min/kg (n = 7), and in Whites compared to Asians, 9.86 ± 3.12 mL/min/kg (n = 20) *vs*. 6.35 ± 2.45 mL/min/kg (n = 7). Due to the small numbers of adult and Asian patients, it is not possible to determine the clinical relevance of these observed differences.

7 Review of Safety

The safety population comprised of 235 patients who have participated in the following six clinical trials:

- MOR-002: phase 1/2 trial (completed)
- MOR-004: phase 3 trial (completed)
- MOR-100: extension trial for MOR-002 (ongoing)
- MOR-005: extension trial for MOR-004 (ongoing)
- MOR-007: ancillary phase 2 trial (ongoing)
- MOR-008: ancillary phase 2 trial (ongoing)

Data from these clinical trials were integrated for the review of safety.

Two hundred twenty-two of 235 (94%) patients were exposed to the proposed marketing dose regimen (elosulfase alfa 2.0 mg/kg QW), with a duration ranging from 1 to 100 weeks. The overall mean (± SD) duration of exposure in all 235 patients was 50.2 (± 37) weeks. Fifty of these patients were treated with elosulfase alfa 2 mg/kg QW for at least 52 weeks.

Of the 235 patients who received at least one dose of elosulfase alfa, 175 (74%) patients experienced an adverse reaction. The most common adverse reactions occurring in ≥10% of patients in the safety population (n=235) 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 five (10.6%) patients experienced a serious adverse reaction. Most serious adverse reactions were acute reactions associated with infusion, such as anaphylaxis or hypersensitivity reactions.

The FDA review team identified a total of 18 (7.7%) cases of anaphylaxis from 235 patients treated with elosulfase alfa. The total number of anaphylaxis cases includes 16 cases identified by the Applicant and 2 additional cases identified during the review of patient narratives. Both patients experienced skin involvement (flushing) and respiratory compromise (dyspnea or cough) during elosulfase alfa infusion, thereby meeting the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) 2006 criteria for anaphylaxis (Table 15).

Table 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, pruritus or 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 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson H et al. J Allergy Clin Immunol 2006;117:391-7.[16]

Signs and symptoms of anaphylactic events observed in elosulfase alfa-treated patients 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 and up to 3 hours after infusion. Anaphylaxis has also occurred as late into treatment as the 47th infusion. It should be noted that all patients in MOR-004 received premedication with antihistamines with or without antipyretics.

16 Sampson H, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

Hypersensitivity reactions were reported in 64 (27%) patients. Most commonly reported hypersensitivity reactions included angioedema, urticaria, peripheral edema, facial edema, wheezing, flushing, cough, dyspnea and rash. One patient discontinued treatment due to anaphylaxis after the tenth infusion of elosulfase alfa, and another patient discontinued treatment after the 45th infusion due to recurrent severe hypersensitivity reactions and anaphylaxis.

8 Immunogenicity

As with all therapeutic proteins, there is a potential for development of immunogenicity. All patients treated with elosulfase alfa 2 mg/kg once weekly in MOR-004 developed anti-drug antibodies by Week 4. By Week 16, approximately 96% of the weekly-treated patients developed neutralizing antibodies capable of inhibiting the drug from binding the mannose-6-phosphate receptor. Binding to this receptor is required for the elosulfase alfa to be taken into cells where it is active.

Antibody titers were sustained or increased for the duration of elosulfase alfa treatment, including the extension phase to 72 weeks. Since the majority of patients developed neutralizing antibodies and neutralizing antibody titers were not assessed, there are currently inadequate data to assess the relationship between antibody development and therapeutic response or occurrence of anaphylaxis or other hypersensitivity reactions. For example, it is not known how long it would take to manifest loss of efficacy due to neutralizing antibody-mediated inhibition of elosulfase alfa uptake into cells or re-accumulation of GAG. The 24-week placebo data from MOR-004 suggest no changes in efficacy for at least 24 weeks without treatment (see Figure 6), and it is unclear how long patients would need to be followed to detect loss of efficacy, particularly if the drug's efficacy is due to mobilization of GAG from cells (i.e., must factor in time to re-accumulation). Another group of MPS patients (i.e., MPS I) who developed immune reactions on enzyme replacement therapy showed declining antibody reactivity by 26 weeks and low antibody titers by 104 weeks.[17] It is not clear whether MPS IVA patients treated with elosulfase alfa will experience similar immune tolerance with continued therapy, as they seem to have sustained or increased antibody titers after 72 weeks of enzyme replacement therapy.

9 References

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