CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125460Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 13, 2014
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA #	125460
Applicant Name	BioMarin Pharmaceutical Inc
Date of Submission	March 29, 2013
PDUFA Goal Date	February 28, 2014
Proprietary Name / Established (USAN) Name	Vimizim/Elosulfase alfa
Dosage Forms / Strength	5 mg/5 mL (1 mg/mL) injection, for intravenous use (Dosing: 2 mg/kg IV once weekly)
Proposed Indication(s)	Patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tamara Johnson, MD
CDTL Review	Jessica Lee, MD
Product Quality (DTP/OBP)	C. Ausin-Moreno, Ph.D., J. Brunelle, Ph.D., and R. Ledwidge, Ph.D.
Product Quality Microbiology (OC/BMAB)	C. Thomas, Ph.D., C. Gomez-Broughton, Ph.D.
Immunogenicity (DTP/OBP)	J. Wang, M.D. (signed by S. Kirshner, Ph.D.)
Nonclinical (DGIEP)	F. Cai, Ph.D. D. Joseph, Ph.D. (secondary review) A. Jacobs, Ph.D. (tertiary review
Clinical Pharmacology (OCP/DCP3)	C. Hon, Pharm.D.
Statistics (DB III)	B. Vali, M.S.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

BioMarin has submitted the following BLA for consideration of the following indication:

1) Vimizim (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

In this BLA, the applicant submits the following single trial for registration of Elosulfase, herein referred to as Vimizim. The BLA consisted of a single pivotal trial, MR-004 which was a 24-week, multinational (17 countries), multicenter (31 clinical sites), randomized, double-blind, placebo-controlled trial in 176 patients with MPS IVA (aged 5 to 57) 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 randomization was stratified by screening 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old). The Primary Endpoint (6-minute walk test [6MWT]) was defined as the change in distance walked in the 6MWT from baseline to Week 24.

2. Background

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, 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.

Mucopolysaccharidosis IV Type A (MPS IVA), or Morquio syndrome Type A, is a rare, lysosomal storage disease due to deficient activity of the lysosomal enzyme N–acetylgalactosamine 6-sulfatase (GALNS). Without the activity of GALNS, 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 175 mutations of the GALNS gene. The GALNS gene mutations include missense mutations (78%), small deletions (9%), nonsense mutations (5%), large deletions (2%) and insertions (2%).[1] The following three missense mutations accounted for over 5% of all mutations: R386C, G301C, and I113F.

[1] Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 253000: 10 January 2011: World Wide Web URL: http://omim.org/

The types of Mucopolysaccharidoses (MPS) are listed below:

Table 1: Types of Mucopolysaccharidoses (MPS)

Reproduced from Medical Officer Summary, Dr. Johnson

Type	Name of Syndrome	Deficient Enzyme	Accumulated Product
MPS I	Hurler Syndrome	A-L-iduronidase	Heparan Sulfate Deramatan
MPS II	Hunter Syndrome	Iduronate sulfatase	Heparan Sulfate Dermatan 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

3. CMC

Elosulfase alfa is supplied as a concentrated solution for infusion (1 mg/mL) requiring dilution with 0.9% normal saline solution prior to administration. The proposed

marketing dose of elosulfase alfa is 2 mg/kg/dose given intravenously (IV) once weekly. The product labeling states that the product should be stored under refrigeration at 2ºC to 8ºC and protected from light.

The Division of Therapeutic Proteins reviewers have recommended approval of BLA 125460, and I agree with their assessments. The reader is referred to the reviews for further details.

CMC/Product Quality Review

The Product Quality reviewers have concluded that the information submitted in the application are adequate to support the conclusion that the manufacture of elosulfase alfa is well-controlled, and leads to a product that is pure and potent. In addition, they have concluded that the stability data support a 24-month expiry. Initial manufacturing issues precluded this expiry initially but these issues have been resolved.

The CMC reviewers including Product Quality have also identified post-marketing commitments to optimize the test methods and to ensure appropriate control of the manufacturing process which are defined in the summary below in **Section 13**. Specific CMC issues worthy of additional comment included the following:

CMC/Immunogenicity Review

The reader is referred to the Immunogenicity review by Dr. J. Wang (signed by S. Kirshner), dated December 13, 2013, for complete information.

All patients treated with elosulfase alfa 2 mg/kg once weekly in the placebo-controlled trial (MOR-004) developed anti-drug antibodies (ADA) by Week 4. By Week 16, approximately 96% of the weekly-treated patients developed neutralizing antibodies (NAb) 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. Anti-drug antibody titers were sustained or increased for the duration of elosulfase alfa treatment, including the extension phase to 72 weeks. The majority of patients developed NAb, but NAb titers were not assessed; therefore, there are currently inadequate data to assess the relationship between antibody development and therapeutic response or occurrence of anaphylaxis or other hypersensitivity reactions. The immunogenicity reviewers recommended certain PMRs for assessment of the developing ADA on clinical safety and efficacy and recommend that NAb titers be determined to assess whether the presence of high titer NAb is correlated with loss of efficacy, as it is with some other treatments. Additional PMRs regarding immunogenicity are discussed below.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical review team has recommended approval, and I agree with their recommendation. The reviewers have not recommended PMCs or PMRs.

5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review by Dr. C. Hon, dated October 28, 2013, for complete information. Dr. Hon considers clinical pharmacology information submitted to support this BLA acceptable, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the labeling.

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this supplemental application because the product is not an antimicrobial product.

7. Clinical/Statistical-Efficacy

The Applicant has submitted a single pivotal trial, MR-004, which was a 24-week, multinational (17 countries), multicenter (31 clinical sites), randomized, double-blind, placebo-controlled trial in 176 patients with MPS IVA (aged 5 to 57) 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 randomization was stratified by screening 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old). The Primary Endpoint (6-minute walk test [6MWT]) was defined as the change in distance walked in the 6MWT from baseline to Week 24. The reader is referred to the Clinical review by Dr. T. Johnson, dated November 26, 2013, and the Statistical review by Mr. B. Vali, dated October 25, 2013, for complete information. Dr. T. Johnson recommends approval of BLA 125460 with the requirement for postmarketing studies to demonstrate durability of clinical benefit and long-term safety with elosulfase alfa treatment. The CDTL, Dr. Lee concurs.

Dr. Lee appropriately discusses that the clinical significance of the measured treatment effect of Vimizim on the 6MWT and its relevance to patients with MPS IVA remains to be confirmed. The regulatory requirement of substantial evidence of effectiveness/clinical benefit requires *adequate and well-controlled clinical studies. These should include the following elements*[2]*:*

- Study should be designed well enough "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation"[3]
- Usual approval standard is two adequate and well-controlled studies

Clinical research in MPS IVA and all diseases should satisfy the same ethical requirements that apply to clinical research generally. People with rare diseases deserve the same protections. Drugs/biologics for rare diseases should meet the same statutory standards of safety and effectiveness that apply to drugs/biologics for more common diseases. It has been determined that the "FDA has determined that it is appropriate to

[2] 21CFR 314.50, 21CFR314.126

exercise the broadest flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness."[3] The Code of Federal Regulations does provide room for flexibility[4] including some components as:

- "While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards"

"The FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information….required to provide for a particular drug to meet the statutory standards." *The data in this application need to be interpreted in light of these regulatory perspectives.*

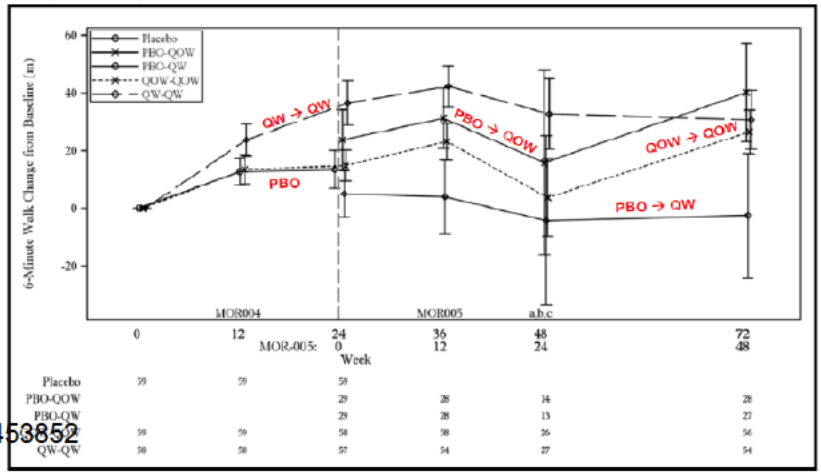
Table 2 represents the results of the Placebo controlled Trial MOR-004 reflecting the mean difference in changes in the primary endpoint, 6 MWT representing statistically significant results. Figure 1 provides data from trial MOR-005 that support the primary endpoint results but raise questions on durability of effect as well as unclear reasons for the lack of benefit in the placebo arm that were switched to QW treatment.

Table 2: Results from the Placebo-Controlled Clinical Trial (MOR-004)

	Elosulfase alfa 2 mg/kg Once Weekly			Placebo			Vimizim vs. Placebo
	Baseline	Week 24	Change	Baseline	Week 24	Change	Mean Difference in Changes
N	58	57*	57	59	59	59	
Six-Minute Walk Test (Meters)							
Mean ± SD	203.9 ± 76.32	243.3 ± 83.53	36.5 ± 58.49	211.9 ± 69.88	225.4 ± 83.22	13.5 ± 50.63	23.0† (CI_{95}, 2.9, 43.1)
Median	216.5	251.0	20.0	228.9	229.4	9.9	22.5‡ (CI_{95}, 4.0, 40.9)
Min, Max	42.4, 321.5	52.0, 399.9	-57.8, 228.7	36.2, 312.2	50.6, 501.0	-99.2, 220.5	(p = 0.0174)‡,§

* One patient in the Vimizim group dropped out after 1 infusion.
† Observed Vimizim mean change – Placebo mean change.
‡ ANCOVA Model-based Vimizim mean change – Placebo mean change, adjusted for baseline 6MWT categories (less than or equal to 200 meters, greater than 200 meters) and age groups (5-11, 12-18, 19 or older).
§ p-value based on the model-based difference in means.

Figure 1 **Mean change in 6MWT in the placebo-controlled trial (MOR004) and the extension trial (MOR005)**



Source: Applicant's response to Information Request, dated September 27, 2013, Figure 14.2.2.1.

These issues were fervently discussed during the review as well as during the Endocrine and Metabolic Advisory Committee. As noted by Dr. Lee, there are potential issues with use of the 6-MWT as an efficacy endpoint. As well the treatment with Vimizim was not associated with sustained efficacy from preliminary analyses of primary endpoints. These data suggest that there is lack of sustained increasing improvement but the potential for maintaining the baseline improvement in these patients may be also a possibility. The contribution of anti-elosulfase antibodies incidence, inhibitory activity and persistence of uptake neutralizing antibodies on these endpoints will be answered with the completion of the outstanding PMRs and discussed below. These issues remain to be elucidated with postmarketing exposures and data collection in these patients.

8. Safety

I concur with Dr. Johnson's medical review of the safety information which is summarized by Dr. Lee in the CDTL summary. Briefly, the reader is referred to the Clinical review by Dr. T. Johnson, complete information. Of concern is the high prevalence of hypersensitivity reactions including anaphylaxis representing the most important adverse reactions associated with elosulfase alfa treatment. These are reflected in the boxed warning and the Warnings and Precautions section of the labeling. As stated below, there are postmarketing requirements to understand better the long term safety of elosulfase alfa treatment. This has direct implications for the under 5 year old pediatric patient with MPS IVA in which efficacy has not been established and is likely a target population for off label use. These issues are addressed below.

9. Advisory Committee Meeting

On November 19, 2013, the Division sought advice from the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) regarding the appropriateness of the 6MWT to assess treatment benefit in this patient population. The majority of the Committee members considered the 6MWT to be adequate for evaluating treatment benefit in MPS IVA patients, since the 6MWT is an integrated measure that is able to show change in this heterogeneous patient population. For further details please see the CDTL summary of Dr. Lee. Although 6-MWT is an assessment of multiple organ systems involved in MPS IVA, I do not agree that the efficacy endpoint completely assesses the impact of Vimizim on the consequences of this disease. It is likely a measure of of some treatment benefit in this patient population but the medical community is encouraged to identify more suitable endpoints for assessment especially in the underserved pediatric population that might be treated off label with this treatment.Until a more appropriate functional measure specific to MPS IVA patients becomes available, one should consider carefully the interpretability of the 6MWT as a definitive measure of clinical benefit.

10. Pediatrics

Elosulfase alfa was granted an orphan product designation on May 15, 2009. Therefore, the regulations that pertain to the Pediatric Research Equity Act (PREA) do not apply to elosulfase alfa. The submission was not presented to the Pediatric Review Committee (PeRC). The Division consulted the Pediatrics and Maternal Health Staff (PMHS) to aid

in the review of the labeling. The reader is referred to the PMHS consultation review by Dr. E. Radden, dated October 21, 2013, for details. The PMHS recommendations have been incorporated into final labeling.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations

The Clinical reviewer selected three clinical sites for inspection, predominantly based on their high enrollment rate. One site was deemed NAI (no action indicated) and two sites had VAI (voluntary action indicated) issues. The reader is referred to the OSI review by Dr. S. Leibenhaut, dated October 24, 2013, for details.

Rare Pediatric Disease Priority Review Voucher Program

The Rare Pediatric Disease Priority Review Voucher (RPDPRV) Program, established under the Food and Drug Administration Safety and Innovations Act (FDASIA), entitles the sponsor of a qualifying rare pediatric disease product application to receive a voucher for 'priority review' of any subsequent human drug application upon marketing approval of the product. The Applicant has submitted data to support that MPS IVA is a rare pediatric disease based on the criteria specified in Section 529 of the Federal Food, Drug, and Cosmetic Act. The Officeof Orphan Products Development (OOPD) has accepted that the prevalence of MPS IVA in the U.S. is less than 200,000, and that no more than 32% of MPS IVA patients would survive beyond 18 years of age. Since the majority of MPS IVA patients would be younger than 18 years of age, the OOPD has determined that MPS IVA meets the FDASIA definition of a rare pediatric disease to be eligible for a voucher. The reader is referred to the OOPD consultation review by Dr. J. Milto, dated January 15, 2014, for complete information. A priority review voucher will be issued at the time of marketing approval.

12. Labeling

Proprietary Name

The Office of Medication Error Prevention and Risk Management determined that the proposed proprietary name "Vimizim" is acceptable. The reader is referred to the Proprietary Name reviews by Dr. D. Baugh, dated July 25, 2013, and Dr. L. Merchant, dated January 13, 2014, for details.

Labeling Consults and Reviews

The Division consulted the Division of Pulmonary, Allergy, and Rheumatology products (DPARP) during the review cycle to seek guidance/recommendations for the boxed warning and the Warnings and Precautions section of the product labeling, with respect to the language regarding anaphylaxis and other hypersensitivity reactions, as the Applicant used the term (b) (4) to describe many of these events. The reader is referred to DPARP consultation review by Dr. T. Kruzick, dated December 4, 2013, for complete information. The DPARP consultant recommended that, due to the difficulty in discerning (b) (4) that may encompass a wide range of clinical events, the term (b) (4) should be avoided. The Applicant was requested to use the 2006 National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) criteria to identify anaphylaxis events, and to separate out

anaphylaxis and hypersensitivity reactions whenever possible. These recommendations are consistent with those outlined in the draft guidance for industry on "Immunogenicity assessment for therapeutic protein products."

Specific Labeling Issues
Key changes to the labeling are summarized below.

Highlights
 A boxed warning for the risk of anaphylaxis was added.
 (b) (4) subsection was eliminated and "Risk of Acute Respiratory Complications" subsection was added to the Warnings and Precautions section.
 The Use in Specific Population section was added to communicate that the safety and effectiveness of Vimizim have not been established in pediatric patients less than 5 years of age.

Full Prescribing Information
 A boxed warning for the risk of anaphylaxis was added.

Section 2: Dosage and Administration
 Four separate subsections were created to simplify the instructions: 2.1 Recommended Dose, 2.2 Preparation Instruction, 2.3 Administration Instruction, and 2.4 Storage and Stability.

Section 5: Warnings and Precautions
 Subsection 5.1 was changed to "Anaphylaxis and Hypersensitivity Reactions", and a separate subsection on (b) (4) was deleted.
 A subsection on "Risk of Acute Respiratory Complications" was added.
 The term (b) (4) was changed to "hypersensitivity reaction".
Section 6: Adverse Reactions
 (b) (4) were deleted.
Section 8: Use in Specific Populations
 Pregnancy category was changed from (b) (4) to C.
 Subsections 8.1 (Pregnancy) and 8.3 (Nursing Mothers) were revised to include clinically relevant animal data for the prescribers (see the PMHS consultation review by Dr. E. Radden, dated October 21, 2013, for details).

 Since data on pediatric patients less than 5 years of age were not reviewed during this review cycle, the (b) (4) was deleted from subsection 8.4 (Pediatric Use). In addition, the following sentence was added to this subsection: "Safety and effectiveness in pediatric patients below 5 years of age have not been established."

Section 13: Nonclinical Toxicology
 (b) (4) was deleted. Clinically relevant nonclinical information was added to "Animal Data" under subsection 8.1.

Section 14: Clinical Studies
- Results on [redacted] (b) (4) were removed from the table.
- [redacted] (b) (4) was deleted.
- A separate subsection on "Extension Trial" was added.

[redacted] (b) (4)
- This section was deleted.

Section 17: Patient Counseling Information
- Subsection on [redacted] (b) (4) was deleted.

- Two new subsections, "Anaphylactic Reactions" and "Morquio A Registry," were added.

In addition to the review team and the DPARP and PMHS consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), Office of Prescription Drug Promotion (OPDP), and the Study Endpoints and Labeling Development (SEALD) Team. Their comments and recommendations have been incorporated into final labeling. For final labeling agreements, the reader is referred to the approved product label for Vimizim.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

All of the review divisions recommended an Approval which gained concurrence from the Clinical reviewer and CDTL. I have concluded that the data in these submissions do reflect a risk and benefit to approve Vimizim for the indication:

> Vimizim (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

The product has a favorable risk/benefit profile for this indication.

13.2 Risk Benefit Assessment:

Vimizim (elosulfase) has been demonstrated to exert a treatment effect on 6-MWT as discussed above. Dr. Lee in her CDTL summary states, "Based on totality of data, I agree with the reviewers that elosulfase alfa should be approved for treatment of MPS IVA. There are currently no products approved for patients with MPS IVA. In light of this medical need, I believe the benefits outweigh the known risks associated with the use of this product. However, additional information is needed to maximize the safe use of this product and prevent increased adverse reactions and potential diminished clinical benefit due to development of neutralizing antibodies. For this reason, the Applicant will be requested to conduct PMR studies to develop appropriate assays and to correlate antibody status with safety and clinical outcome. In addition, a prophylactic immune tolerance regimen should be evaluated in patients who are at high risk of developing persistent neutralizing antibodies."

I do concur with Dr. Lee on this assessment with the following provisos. The exact role of immunoprophylaxis was discussed fervently during this review. Dr. Amy Rosenberg has noted that "it is thus crucial to understand the relationships between genetic mutations, endogenous residual enzyme proteins (cross-reactive immunologic material), development of neutralizing antibodies and their impact on clinical outcomes of lysosomal storage diseases. For patients in whom neutralizing antibodies may cause severe adverse clinical outcomes, it is paramount to develop tolerance inducing protocols to preclude, where predictable, or treat such life-threatening responses"[5]. She has noted that the "Consequences and probability of immune responses to therapeutic proteins determine course of action; risk assessment should also include the risk associated with the tolerance inducing therapy. When consequences are life threatening and probability of occurrence is high, tolerance induction is indicated: may necessitate "high risk" tolerance protocols. Tolerance induction should be considered when the immune response abolishes efficacy of highly effective (but not necessarily life-saving) therapeutics: also consider risks of tolerance regimens and potential impact of tolerance regimen on underlying disease." These issues have been discussed as part of this application review. Is therapeutic efficacy an endpoint that if compromised by antibody development be addressed through tolerance regimens? Tolerance induction is indicated prophylactically when a patient's genetic status is known to pose a very high risk for development of high titer/neutralizing antibody or anaphylaxis. Dr. Rosenberg as stated that "Tolerance induction should be considered and further evaluated in a risk based manner in clinical studies of mAbs in concordance with clinical efficacy and safety studies. Short course of tolerance therapy, per Pompe prophylaxis, at the outset of mAb treatment, may prove efficacious, while avoiding serious infectious/malignant consequences of more prolonged therapy." The exact role of this type of treatment for MPS IVA remains a goal for elucidation and is discussed below in the prospective request for the PMRs outlined below. The future discussion will be broad based and target the lysosomal enzyme diseases and reflected in the immune responses to replacement of lysosomal enzymes as outlined below by Rosenberg and colleagues[6].

Table 1 Immune responses to replacement lysosomal enzymes

Disease	Product	Enzyme	Product status	Patients with IgG antibody (%)	Reference
Gaucher's	Ceredase	Alglucerase	Licensed	12.8	18
	Cerezyme	Imiglucerase	Licensed	13.8	Product label
Fabry's	Fabrazyme	Agalsidase beta	Licensed	90	20
Hurler's (MPS I)	Aldurazyme	α-L-iduronidase	Licensed	91	55
Pompe's	Myozyme	Acid-α-glucosidase	Licensed	89	Product label
Hunter's (MPS II)	Elaprase	Iduronate-2-sulfatase	Licensed	51	Product label
Maroteaux-Lamy (MPS VI)	Naglazyme arylsulfatase B	*N*-acetylgalactosamine-4-sulfatase	Phase 3 completed	97	87

MPS, mucopolysaccharidosis.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
There are no requirements for postmarketing risk evaluation and mitigation strategies.

[5] Wang J, Lozier J, Gibbes Johnson G et al**. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention and treatment.** Nature biotechnology 2008;26;901-908.

[6] Ibid.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to 1) identify an unexpected serious risk of anaphylaxis and hypersensitivity reactions associated with long term exposure to Vimizim (elosulfase alfa), 2) identify an unexpected serious risk of adverse maternal, neonatal or infant outcomes associated with Vimizim (elosulfase alfa) exposure during pregnancy, and 3) identify an unexpected serious risk of immune-mediated disorders associated with the development of anti-drug antibodies, including neutralizing antibodies, associated with long term exposure to Vimizim (elosulfase alfa).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1 Evaluate the long-term safety of Vimizim in adult and pediatric patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. Include incidence rate calculations as part of long-term safety evaluation assessments to monitor and characterize risk of exposure to Vimizim. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time to orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted every 6 months. Patients previously enrolled in clinical trials MOR-005 and MOR-007 may be rolled over to this study but will be monitored using the MOR-005 and MOR-007 protocols, respectively.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2014
Final Protocol Submission (Updated Final Protocol for MOR-005)	12/2014
Final Protocol Submission (Updated Final Protocol for MOR-007)	03/2015
Interim Report Submission:	09/2017
Interim Report Submission (Report for MOR-007):	03/2018
Interim Report Submission:	09/2019

Interim Report Submission (Report for MOR-005):	03/2020
Study Completion:	09/2024
Final Report Submission:	03/2025

2 Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibits binding to the mannose-6-phosphate receptor. The final report will contain a summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay Standard Operating Procedure (SOP). This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs 1 3, and 6.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2015

3 Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Final Report Submission: 3/2016

4 Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs 1, 5, and 6.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Final Report Submission: 3/2015

5 Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Final Report Submission: 3/2016

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected risk of serious infection in patients receiving treatment with Vimizim (elosulfase alfa) and an immune tolerance regimen.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

6 Evaluate the occurrence of serious infections associated with administration of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim (elosulfase alfa) who are at high risk of developing persistent neutralizing antibodies. This immune tolerance regimen will be implemented before or concomitant with the onset of Vimizim (elosulfase alfa) therapy.

The timetable you submitted on DATE, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2016
Trial Completion:	03/2020
Final Report Submission:	09/2020

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

7 To develop and implement, as a release and stability test method, a potency assay that measures the K_m and k_{cat} of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion:	06/2015
Final Report Submission:	09/2015

8 To revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between (b) (4) peak. The revised specification together with the validation report will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion:	06/2015

Final Report Submission: 09/2015

9 To demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in a side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion: 09/2014
Final Report Submission: 01/2015

10 To include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion: 06/2014
Final Report Submission: 09/2014

11 To include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion: 06/2014
Final Report Submission: 09/2014

12 To add cellular uptake as a release assay for drug product and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2014

13 Conduct studies to understand the mechanism of low endotoxin recovery in the formulated bulk drug substance and drug product. These studies should

investigate the endotoxin degradation or association pathway and determine whether or not depyrogenation is reversible (and if so, the conditions under which depyrogenation is reversible). Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion: 09/2014
Final Report Submission: 01/2015

14 Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC 1224 M.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2014

15 Conduct an additional study comparing rabbit pyrogen and LAL test results. The study should include formulated bulk drug substance spiked with 20 EU/ml and 100 EU/ml endotoxin. The time points and controls should be the same as for the previous studies.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion: 11/2014
Final Report Submission: 01/2015

16 Provide results from protocol PVP-101037 (b) (4) to be executed during the 2014 manufacturing campaign.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Study Completion: 03/2015
Final Report Submission: 06/2015

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW E MULBERG
02/13/2014
Deputy Director Summary Review