

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125561Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 6, 2015
From	Jessica J. Lee, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125561
Supplement#	N/A
Applicant	Alexion Pharmaceuticals Inc.
Date of Submission	January 8, 2015 (rolling submission began October 21, 2014)
PDUFA Goal Date	December 8, 2015 (review clock extended by 3 months due to a major amendment)
Proprietary Name / Established (USAN) names	KANUMA / sebelipase alfa
Dosage forms / Strength	20 mg/10 mL (2 mg/mL) injection, for intravenous use <u>Dosage:</u> <i>Rapidly progressive LAL deficiency presenting within first 6 months of life – starting dosage 1 mg/kg IV once weekly; if optimal clinical response not achieved, increase to 3 mg/kg once weekly</i> <i>Pediatric and adult patients with LAL deficiency - 1 mg/kg IV every other week</i>
Proposed Indication(s)	Treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency
Recommended:	<i>Approval pending resolution of the issues identified during facility inspection of the drug product fill and finish site</i>

1. Introduction

Kanuma (sebelipase alfa) is a recombinant form of human lysosomal acid lipase (rhLAL) enzyme, produced in the egg white of genetically engineered chickens (*Gallus gallus*). Because genetically engineered chickens are used to produce the bulk processed rhLAL that is purified as part of the CDER-regulated drug substance manufacturing process, approval of a new animal drug application (NADA) from the Center for Veterinary Medicine (CVM) is required prior to BLA approval. CVM regulates the recombinant DNA (rDNA) construct in a lineage of genetically engineered chickens to ensure that rhLAL protein (intended for the treatment of humans) is present in their egg whites (the starting material for the manufacture of human drug product rhLAL).

Sebelipase alfa received orphan drug designation on July 1, 2010 and Fast Track designation on June 14, 2011. It received Breakthrough Therapy designation on May 13, 2013 for the rapidly progressive phenotype (i.e., Wolman disease), (b) (4)

On January 8, 2015, Alexion Pharmaceuticals Inc. (the Applicant)¹ notified the Agency that it has completed its rolling submission of a biologics license application (BLA), including all requested information from the CVM to initiate their review, to support marketing approval of Kanuma for the treatment of lysosomal acid lipase (LAL) deficiency.

Results from two clinical trials, an open-label, historically-controlled trial in infants with rapidly progressive disease and a double-blind, placebo-controlled trial in pediatric and adult patients with LAL deficiency, were submitted to BLA 125561 to support the following indication:

“Kanuma is indicated (b) (4) for patients with Lysosomal Acid Lipase (LAL) deficiency.”

This BLA was reviewed as part of “the Program” under the Prescription Drug User Fee Act (PDUFA) V. The review of this application was conducted as Priority review. However, a major amendment was received on September 2, 2015, and the PDUFA review clock was extended by 3 months on September 3, 2015 to permit time for review of the additional material.

All the review disciplines recommend approval; however, they have recommended several post-marketing commitment studies to address long-term efficacy and safety, and to optimize the control strategy for the product. I agree with the review disciplines that the data provided in the BLA are adequate to support approval of sebelipase alfa for the treatment of LAL deficiency. However, the facility inspection of the drug product fill and finish site was classified as official action indicated (OAI) due to multiple cGMP issues, including (b) (4); therefore, I recommend approval pending resolution of the issues identified during facility inspection.

This memo summarizes the information contained in BLA 125561 and discusses the recommendations made by each review discipline.

2. Background

Clinical background

Lysosomal acid lipase (LAL) deficiency, a rare autosomal recessive lysosomal storage disorder caused by mutations in the lysosomal acid lipase (*LIPA*) gene, results in absent or low levels of LAL enzyme activity.² Since LAL is responsible for hydrolysis of cholesteryl esters and triglycerides into free cholesterol, glycerol, and fatty acids, its deficiency results in accumulation of cholesteryl esters and triglycerides in lysosomes of the gastrointestinal tract, liver, spleen, and cardiovascular system.³ The diagnosis of LAL deficiency is based on *LIPA* gene sequencing and the measurement of LAL levels in peripheral blood leukocytes.

¹ Synageva BioPharma Corp. submitted the BLA, but it transferred all rights for BLA 125561 to Alexion Pharmaceuticals Inc. during the review cycle (on June 23, 2015).

² <http://www.omim.org/entry/278000>

³ Bernstein DL, et al. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. *J Hepatol* 2013;58:1230-43.

There are two phenotypes of LAL deficiency: (1) Wolman disease, characterized by absence of LAL enzyme activity, and (2) cholesteryl ester storage disease (CESD), characterized by partial LAL enzyme activity. Wolman disease, a very rare condition with an estimated incidence of 1 in 500,000 live births, is an early-onset fulminant disease presenting during infancy with massive infiltration of the liver, spleen, and other organs by macrophages filled with cholesteryl esters and triglycerides. Patients with Wolman disease typically present at 2 to 4 months of age with growth failure, marked hepatosplenomegaly, and intestinal failure. Other features may include anemia, hypertriglyceridemia, liver dysfunction, and adrenal calcification. Survival beyond the first year of life is highly unusual. Median time between diagnosis and death is approximately 1.3 months, with severe malnutrition and liver failure as key contributors to mortality.

CESD, with an estimated prevalence between 1/40,000 and 1/300,000 depending on the geographic location,⁴ is a milder, later-onset disorder presenting most commonly with elevated serum transaminases, dyslipidemia (high LDL-cholesterol [LDL-c], high triglycerides, and low HDL-cholesterol [HDL-c]), and hepatosplenomegaly. Because diagnosis typically requires a high index of suspicion, CESD is believed to be an under-recognized condition.⁴ Complications of CESD include hepatic fibrosis with progression to cirrhosis and accelerated atherosclerosis, though clinical outcomes and disease progression are highly variable, with survival typically into adulthood. Liver biopsies of the affected patients have evidence of microvesicular steatosis, which can progress over time to fibrosis, cirrhosis, and eventually liver failure and death.³ Life expectancy of patients with CESD depends on the severity of disease and associated complications.

Although many CESD patients are diagnosed with dyslipidemia, it is often misdiagnosed and recognized less frequently than the complications of liver disease related to LAL deficiency.⁴ Accumulation of neutral fats and cholesteryl esters in the arteries predispose affected persons to atherosclerosis, and hypercholesterolemia is common. Premature accelerated atherosclerosis has been described in case reports of CESD patients, and include coronary artery disease, aneurysm, stroke, atherosclerosis of the aorta and stenosis of femoral arteries.⁵ Other than biochemical abnormalities, patients with CESD are largely asymptomatic.

In order to better understand the signs and symptoms that are most bothersome to patients with CESD, the clinical review team participated in a listening session on February 27, 2015, where two CESD patients and two parents with children with CESD shared their experiences with the disease. The most bothersome signs and symptoms reported by them were large abdomen and fatigue. They also expressed their concerns with the presence of liver fibrosis and/or the impact of high cholesterol levels.

There is currently no approved treatment for LAL deficiency. Treatment of LAL deficiency is limited to control of cholesterol levels and to prevent premature atherosclerosis through dietary modifications and use of lipid-lowering medications.

⁴ Reiner Z, et al. Lysosomal acid lipase deficiency-An under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis* 235 (2014) 21-30.

⁵ Elleder M, et al. Subclinical course of cholesteryl ester storage disease in an adult with hypercholesterolemia, accelerated atherosclerosis, and liver cancer. *J Hepatol* 2000;32:528-34.

Sebelipase alfa is intended to provide exogenous enzyme rhLAL that will catalyze the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids. As a replacement for LAL, sebelipase alfa is taken up by cells through receptor-mediated endocytosis (via mannose receptors, mannose-6-phosphate [M6P] receptors or both, depending on the cell/tissue type) and subsequent transportation to lysosomes where it compensates for the function of the native enzyme.

Regulatory Background

Sebelipase alfa was developed under IND 108460, and genetically engineered chickens (*Gallus gallus*) expressing human lysosomal acid lipase in their egg white was developed under Investigational New Animal Drug (INAD) file I-011919.

Pertinent pre-submission regulatory issues and meetings are summarized chronologically below:

- July 1, 2010: Orphan product designation was granted.
- December 22, 2010: The Applicant submitted New IND (#108460) for SBC-102 (sebelipase alfa).
- June 14, 2011: Fast Track designation was granted.
- June 12, 2012: An End-of-Phase 1 (EOP-1) meeting was held to discuss the clinical development plan for sebelipase alfa. The Division recommended reviewing the data from two natural history studies (LAL-1-NH01 and LAL-2-NH01) to inform the endpoints, target population, trial duration, and design of future clinical trials. The Division did not agree that the Applicant provided adequate data (b) (4)
- November 6, 2012: A Type C meeting was held as a follow-up to the EOP-1 meeting to discuss the path forward for clinical development. The Division reiterated concerns over the use of ALT as a primary endpoint in patients with late-onset LAL deficiency since the data provided were considered insufficient to support ALT as a valid surrogate endpoint for clinical benefit in patients with CESD. The Division stated that, to support the use of ALT as a primary endpoint, it would be important to demonstrate that liver enzyme elevation is on the causal pathway of the disease and does not simply correlate or behave as an "innocent bystander" to the disease process. The Division provided an example that, if all LAL-deficiency patients who have a certain pre-specified level of increase of ALT go on to develop end-stage liver disease and all patients who have their ALT reduced to below that threshold with treatment are no longer at risk of developing end-stage liver disease, then ALT could potentially serve as a surrogate endpoint.
- May 13, 2013: Breakthrough Therapy designation was granted for Wolman disease (b) (4)

(b) (4)

- February 12, 2014: Type B pre-BLA CMC meeting was held to discuss the CMC requirements to support BLA submission and CVM's NADA requirements. During the meeting, CDER, CVM, and the Applicant agreed that the point of separation between CVM and CDER regulations is the point of collection of the contents of the eggs from the genetically engineered chickens.
- February 25, 2014: Type B Post-Breakthrough Therapy meeting was held to discuss the proposed clinical data intended to support product labeling for sebelipase alfa. The Division again communicated to the Applicant that serum ALT is not considered to be an established biomarker that predicts clinically meaningful treatment benefit in LAL deficiency or a surrogate endpoint that is reasonably likely to predict clinical benefit under the Accelerated Approval Pathway. Therefore, the Division recommended that the Applicant prioritize drug development program for infantile-onset LAL deficiency, and submit an efficacy supplement to broaden the indication to include the late-onset patients once adequate data have been obtained to demonstrate improved clinical outcome in this subgroup.
- August 15, 2014: A Pre-BLA meeting was planned but cancelled by the Applicant after receipt of the preliminary meeting comments. Preliminary meeting responses included a recommendation that the efficacy assessments in the BLA focus on data from infantile-onset patients with LAL deficiency, with supportive data from children and adults with LAL deficiency (i.e., CESD). The Division again communicated they remain concerned that the proposed clinical trial endpoint for late-onset LAL deficiency neither directly measures clinical benefit of treatment (i.e., how a patient feels, functions or survives) nor represents a surrogate endpoint reasonably likely to predict clinical benefit. In addition, the Division stated that the review clock will not begin until the Applicant informs the Agency that a complete BLA has been submitted. A complete BLA includes all requested information from the Center for Veterinary Medicine (CVM) to evaluate the first regulated article (i.e., a recombinant DNA construct engineered to express recombinant human lysosomal acid lipase in the egg white of genetically engineered chickens) to support the new animal drug application (NADA).
- October 21, 2014: The Applicant began rolling submission of BLA 125561 with submission of key nonclinical, clinical, and quality components on October 21, 2014 and November 21, 2014.
- January 8, 2015: BLA was considered fully submitted once the outstanding components required by the CVM were submitted.

On June 23, 2015, Synageva BioPharma Corp. transferred all rights for BLA 125561 to Alexion Pharmaceuticals Inc. The Applicant stated that there will be no changes in the manufacturing process, facilities, or quality oversight for sebelipase alfa associated with the acquisition.

On June 25, 2015, the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending marketing authorization of Kanuma (sebelipase alfa), and granted the request for accelerated assessment. Kanuma subsequently received marketing authorization from the European Commission on September 1, 2015. In addition, a New Drug Application (NDA) for sebelipase alfa was submitted to Japan's Ministry of Health, Labour and Welfare (MHLW) on May 26, 2015.

Submission and Review

The original BLA was fully submitted on January 8, 2015, and the application was granted a Priority Review status with a PDUFA goal date of September 8, 2015. Upon receipt of a major amendment on September 2, 2015, the PDUFA review clock was extended by 3 months on September 3, 2015 to permit time for review of the additional material.

All of the relevant review disciplines have written review documents. The primary review documents relied upon in my CDTL review are listed below:

Review discipline	Name(s) of reviewers
Product Quality (DBRR II/OBP) - Drug Substance - Drug Product - Secondary review	C. Downey, Ph.D. (Lead) and S. Williams, Ph.D. (Assay Validation), dated 6/9/2015; an addendum by C. Downey, Ph.D., dated 7/31/2015 A. Arudchandran, Ph.D., dated 6/8/2015 J. Liu, Ph.D., dated 6/22/2015
Immunogenicity (DBRR III/OBP)	J. Pedras-Vasconcelos, dated 6/9/2015
Product Quality Microbiology (DMA/OPF/OPQ) - Drug Substance - Drug Product	B. Chi, Ph.D., dated 6/10/2015 and 8/21/2015 (addendum) C. Thomas, Ph.D., dated 6/12/2015 and 8/24/2015 (addendum)
Nonclinical (DGIEP) - Primary review - Tertiary review	T. Chakraborti, Ph.D., dated 6/8/2015 A. Jacobs, Ph.D., dated 5/14/2015
Clinical Pharmacology (DCP-3/OCP)	J. Fang, Ph.D. and Sarah Dorff, Ph.D., dated 6/10/2015
Clinical (DGIEP) - Wolman disease - Cholesteryl ester storage disease	L. Weintraub, M.D. (Dr. Weintraub's review has not be finalized at the time of completion of this CDTL review) J. Tomaino, M.D., dated 6/8/2015
Statistics (DB III)	B. Vali, M.S., dated 6/12/2015
Clinical site inspections (DCCE/OSI)	S. Leibenhaut, M.D., dated 6/22/2015
Consultation review (DAVP) - Liver endpoints - Virology	P. Mishra, M.D., dated 6/1/2015 L. Mishra, Ph.D., dated 5/28/2015 and 6/1/2015
Consultation review (DMEP)	J. Golden, M.D., dated 4/29/2015
Consultation review (DPMH) - Pediatrics - Maternal Health	E. Hausman, M.D., dated 5/12/2015 L. Sahin, M.D., dated 6/9/2015
Consultation review (OOPD)	J. Milto, M.D., dated 5/14/2015
Proprietary name review (DMEPA)	M. Barlow, R.N., dated 12/9/2014
Labeling review (DMEPA)	M. Barlow, R.N., dated 4/14/2015
Labeling review (OBP)	J. Abdus-Samad, Pharm.D., dated 8/13/2015
Labeling review (OPDP)	A. Adeleye, Pharm.D., dated 6/3/2015

DBRR II, Division of Biotechnology Review and Research-II; OBP, Office of Biotechnology Products; DMA, Division of Microbiology Assessment; OPF, Office of Process and Facilities; OPQ, Office of Pharmaceutical Quality; DGIEP, Division of Gastroenterology and Inborn Errors Products; ODE III, Office of Drug Evaluation-III; OCP, Office of Clinical Pharmacology; DCP-3, Division of Clinical Pharmacology 3; DB III, Division of Biometrics III; DCCE, Division of Clinical Compliance Evaluation; OSI, Office of Scientific Investigations; DAVP, Division of Antiviral Products; DMEP, Division of Metabolism and Endocrinology Products; CDRH, Center for Devices and Radiological Health; DPMH, Division of Pediatric and Maternal Health; OOPD, Office of Orphan Products Development; DMEPA, Division of Medical Error Prevention and Analysis; OPDP, Office of Prescription Drug Promotion.

The reader is referred to the primary review documents for more specific details of the application and review conclusions. This memo summarizes selected information from the primary review documents.

3. CMC

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL). Lysosomal acid lipase is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids.

Sebelipase alfa is produced by recombinant DNA technology and expressed in the oviducts of genetically engineered (GE) chickens (known as SBC LAL-C chickens). The GE chickens lay eggs that include sebelipase alfa in the egg white, and the sebelipase alfa drug substance is purified from these egg whites. The “first regulated article” for this product is the recombinant DNA (rDNA) construct in a lineage of GE chickens, which must be reviewed and approved under administrative new animal drug application (NADA) by the Center for Veterinary Medicine (CVM). Because the GE chickens are source of the unprocessed bulk used in the drug manufacturing process, CVM’s approval decision must temporally precede CDER’s approval of the BLA for commercial therapeutic use of the sebelipase alfa derived from these chickens. In the February 12, 2014 CMC pre-BLA meeting, CDER, CVM, and the Applicant agreed that the point of separation between CVM and CDER regulations is the point of collection of the contents of the eggs from the genetically engineered chickens. Consequently, it was determined that the harvest of egg whites from whole eggs (“egg crack”) is part of the drug substance manufacturing process regulated by CDER, and the egg whites are the starting material for drug substance manufacture regulated under the BLA.

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Based on the review of the submissions under INAD 011919, the CVM reviewers have concluded that:

- 1) the rDNA construct encodes human LAL sequence and, when integrated in the genome of SBC LAL-C chicken, is capable of expressing recombinant rhLAL;
- 2) the rDNA construct is safe to the target animal;
- 3) aside from the GE trait intentionally introduced, SBC LAL-C chickens are phenotypically similar to non-GE chickens;
- 4) the rDNA construct is stably integrated and inherited in a Mendelian fashion across multiple generations;
- 5) there is no significant impact on the environment based on the environment assessment, since the animals and their potentially edible products will be sufficiently physically contained and disposed of by incineration;
- 6) animal husbandry, containment, personnel, and record keeping are sufficient to ensure safety and security of the GE animal and animal products (e.g., eggs, waste, etc.);
- 7) there is adequate assurance that SBC LAL-C chickens will not enter the food supply, and in the event of an inadvertent release CVM has determined that it would have a low level⁶ of concern regarding food consumption risk, and has established an analytical method to determine if any chicken-derived product is from SBC LAL-C chickens;

⁶ For biopharm animals (GE animals that produce medical products) of species traditionally consumed as food, CVM determines food safety risk based on whether the concern level in the event that edible products derived from the animals enter the food supply is low, moderate, or high.

- 8) the sponsor has validated the claim that egg whites of eggs laid by SBC LAL-C chickens contain rhLAL; and
- 9) a rigorous postmarket record-keeping and reporting program has been developed.

For additional details regarding CVM's assessment of the rDNA and GE chickens, the reader is referred to the CVM reviews under INAD 011919.

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Sebelipase alfa is taken up by cells through receptor-mediated endocytosis and subsequently transported to lysosomes where it compensates for the function of the native enzyme. Depending on the cell/tissue type, cellular uptake is mediated by mannose receptors, mannose-6-phosphate (M6P) receptors, or both. Mannose receptors are expressed on the surfaces of cells of reticuloendothelial system, such as Kupffer cells in the liver. M6P receptors are expressed in a variety of cell types and, therefore, may be a more general mechanism for uptake and lysosomal localization. Once transported to lysosomes, sebelipase alfa cleaves cholesteryl esters and triglycerides from endocytosed lipoproteins.

Sebelipase alfa is supplied as a solution for intravenous infusion (2 mg/mL) requiring dilution with 0.9% Sodium Chloride Injection prior to administration (final concentration of 0.1 mg/mL to 1.5 mg/mL). The product labeling states that the product should be stored under refrigeration between 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

The Product Quality reviewers have recommended approval of BLA 125561, and I agree with their assessments. I have summarized the key review findings below.

CMC/Product Quality Review

The reader is referred to the Product Quality reviews by Drs. C. Downey and S. Williams (Drug Substance and Assay Validation) dated June 9, 2015, A. Arudchandran (Drug Product) dated June 8, 2015, J. Liu (Secondary review) dated June 22, 2015, and C. Downey (CMC review addendum) dated July 31, 2015 for complete information.

Sebelipase alfa (rhLAL) is produced in the egg whites of eggs laid by genetically engineered chickens. As stated previously, the CDER-regulated drug substance manufacturing process begins with cracking of eggs and separation of egg yolk from the egg white, and the egg whites serve as the starting material for downstream purification.

The Product Quality reviewers have determined that the data submitted in the application are adequate to support that the manufacturing process of sebelipase alfa is well-controlled and leads to a product that is pure, potent, and stable under the Applicant's proposed storage conditions. In addition, there is sufficient testing to ensure batch-to-batch consistency of purity, potency, and stability. They determined that the drug substance and drug product are free of known endogenous and adventitious infectious agents and meet the parameters recommended by the Agency. There is sufficient virus testing to prevent egg white with high viral load from entering the manufacturing process, and the manufacturing process provides adequate levels of inactivation or removal of viruses not detected by the initial viral testing. They have recommended approval of the BLA, pending adequate response to the deficiencies

identified during inspection of the facilities. See the subsection on “Facilities review/inspection” of this document for details.

(b) (4)

The reviewers have determined that the critical raw materials of animal origin, eggs and egg whites, are tested adequately for adventitious agents. The chickens and eggs are tested monthly for salmonella, various strains of mycoplasma, and viruses known to be human pathogens. In addition, pooled egg whites are tested for relevant vertically transmissible (i.e., chickens-to-eggs) viruses, selected transmissible human viruses (Avian Influenza A and West Nile) and mycoplasma. They are also tested for unknown viruses using a cell-based *in vitro* adventitious agents assay. The reviewers have concluded that the Applicant’s virus control strategy and clearance steps are adequate to remove or inactivate contaminating viruses to support viral safety of the product.

(b) (4)

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addition, the Applicant has implemented measures to minimize exposure of rhLAL to these conditions.

The potency assays of sebelipase alfa consist of two types of assays, enzyme activity and affinity to mannose receptor or mannose-6-phosphate (M6P) receptor.

(b) (4)

Although the reviewers have determined that the current assays are sufficient to control potency to support marketing approval, they recommend implementation of additional assays post-market to enhance control.

(b) (4)

Based on review of the stability data, the Product Quality reviewers recommend a (b) (4)-month expiry for drug substance and a 24-month expiry for drug product when stored at 2°C to 8°C. In-use stability study results indicate that sebelipase alfa is stable for up to (b) (4) hours after dilution.

The Product Quality reviewers have determined that this product meets the criteria for categorical exclusion from preparing an environment assessment under 21 CFR 25.31(c), as the expected introduction concentration (EIC) is minimal (b) (4) ppb into the aquatic environment per year) and will not significantly affect the concentration or distribution in the environment of lysosomal acid lipase, its metabolites, or its degradation products.

Although critical product quality attributes have been tested and controlled to ensure the efficacy, purity, and stability of the product, the Product Quality reviewers have pointed out that due to the rapid product development as a Breakthrough Therapy product, many of the assays have not been fully optimized. Accordingly, they have recommended the following post-marketing commitment (PMC) studies to optimize the test methods and to ensure appropriate control of the manufacturing process:

Drug Substance Quality

1. Characterize the potential levels of (b) (4)
2. Develop and implement a drug substance release test to quantify the percent compositions of the N-terminal variants.
3. To improve control of the N-linked glycan profile, identify for the current HPAEC-PAD method peaks representative of (b) (4) and establish drug substance release specifications for the critical peaks or groups of peaks. Alternatively, develop an alternative method with better resolution to control the glycan profile, such as (but not limited to) the (b) (4) characterization tests.
4. Conduct studies to improve the formulation to reduce or eliminate the potential for formation of visible proteinaceous particles and other insoluble protein aggregates. If a significantly improved formulation is identified, develop the improved formulation for the commercial product.

Drug Product Quality

5. Develop and implement an improved SDS-PAGE or another purity test to quantitate high molecular weight product-related species with greater sensitivity and precision than the current SDS-PAGE method.
6. Implement the (b) (4) test method for drug product release specifications.
7. Implement an assay for uptake of sebelipase alfa into (b) (4) for drug product release specifications.
8. Develop and implement a (b) (4) receptor binding assay for drug product release specifications.
9. Conduct studies to determine whether the (b) (4) receptor binding assays

- are stability-indicating. Implement the stability-indicating assays into the drug product stability specifications with acceptance criteria supported by stability data.
10. Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent values for specific activity.
 11. Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses.
 12. Conduct worst-case simulated or worst-case real world shipping studies for both the drug substance and the drug product to assess the potential impact of shipping conditions on product quality.
 13. Characterize the potential of rhLAL to form oxidized variants and deamidated variants and determine whether variants identified are stability-indicating. Implement changes to the drug substance and drug product control strategies as warranted by the data.

CMC/Product Quality Microbiology Review

The reader is referred to the Product Quality Microbiology reviews by Drs. B. Chi (Drug Substance) dated June 10, 2015 and addendum dated August 21, 2015, and C. Thomas (Drug Product) dated June 12, 2015 and addendum dated August 24, 2015 for complete information.

Dr. Chi reviewed the application for microbial control of the drug substance manufacturing process, including the adequacy of the in-process bioburden and endotoxin monitoring. Based on review of the data, Dr. Chi concluded that the microbial control of the drug substance manufacturing process is adequate in general and has recommended approval of the BLA. However, she indicated that the sensitivity of some of the in-process bioburden tests could be improved with increased test volumes. In addition, qualification of the in-process samples for bioburden and endotoxin tests has not been completed due to sample availability. Dr. Chi has recommended that PMC studies be conducted to address these issues.

Information and data provided in the BLA also indicated that low endotoxin recovery was observed from samples of the unformulated drug substance, (b) (4) and drug substance spiked with endotoxin, indicating that the USP endotoxin method may not be able to detect the presence of contaminating endotoxin. However, the Applicant demonstrated that a modification of the USP method involving (b) (4) sample treatment may be effective in enabling the recovery of endotoxin from spiked samples. The validation of the endotoxin method using an (b) (4) sample treatment will be conducted as a PMC study. In the interim, the rabbit pyrogen test will be used for drug product release to ensure patient safety.

Dr. Thomas reviewed the application for microbial control of the drug product manufacturing process and for assurance of drug product sterility and non-pyrogenicity. She indicated in her review dated June 12, 2015, that she had not found approvability issues to date; however, additional data were needed in order to complete the review. (b) (4)

(b) (4)
Additional data were reviewed in Dr. Thomas' addendum dated August 24, 2015. (b) (4) the release test method was switched to the rabbit pyrogen test. (b) (4)

(b) (4), every drug product lot manufactured thus far for clinical or commercial use has also been subjected to rabbit pyrogen testing. There have been no failures to date. Hence, Dr. Thomas concluded that rabbit pyrogen testing is acceptable for use for drug product release until a more suitable *in vitro* method is developed and validated (through post-marketing commitment).

In summary, the Product Quality Microbiology reviewers determined that BLA 125561 included sufficient data to support microbial control of the drug substance manufacturing process and sterility assurance of the drug product. Their reviews did not identify issues that would preclude approval; both Drs. B. Chi and C. Thomas recommend the product for approval. However, they recommend the following PMC studies to further optimize the manufacturing process and sterility assurance of sebelipase alfa:

Drug Substance Quality Microbiology

1. Increase the bioburden test volume for (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.
2. Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.
3. Improve the endotoxin method for the (b) (4) samples by optimizing the endotoxin test procedures.
4. Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the (b) (4) and drug substance endotoxin test using the modified endotoxin method involving the use of (b) (4) sample preparation system. Provide the validation information and data.

Drug Product Quality Microbiology

5. [REDACTED] (b) (4)
6. Validate the [REDACTED] (b) (4)
[REDACTED]
If the [REDACTED] (b) (4) is revised based on the validation study, update the BLA file accordingly.
7. The microbial retention study [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
8. Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial

- ingress. The study should be performed with a range of small defect sizes (b) (4). Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.
9. (b) (4)
10. Conduct studies to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

Facilities review/inspection

A CVM-led inspection of the Synageva BioPharma in Holden, MA facility was conducted on January 20 - 21, 2015. (b) (4)

(b) (4). The inspection found the handling and security of the animals and the egg harvest procedure satisfactory, and no 483 form was issued. However, a subsequent inspection by the ORA's New England district office in February 2015 resulted in issuance of a 483 form with 8 observations, mainly concerning inadequate microbial control and monitoring and practices preventing microbial contamination. The Applicant has since responded to the 483 items, and the final classification is voluntary action indicated (VAI).

A pre-approval inspection of (b) (4) was conducted on (b) (4). This facility conducts commercial manufacture of the sebelipase alfa drug substance, (b) (4). A 483 form with 11 observations was issued at the conclusion of the inspection for observations related to (but not limited to) (b) (4).

(b) (4) The final classification of the inspection is VAI.

An inspection of (b) (4) was conducted on (b) (4). This facility is responsible for the fill and finish of the drug product. A 483 form with 11 observations was issued at the conclusion of the inspection for observations related to (but not limited to) (b) (4).

(b) (4) The 483 items were sufficiently serious to rise to a classification of official action indicated (OAI). At the time of completion of this

review, the Applicant and (b) (4) are working to address the cGMP issues identified at (b) (4) with the help of third parties.

The remaining facilities were considered to be acceptable; that is, either VAI or no action indicated (NAI).

CMC/Immunogenicity Review

The reader is referred to the Immunogenicity review by Dr. J. Pedras-Vasconcelos, dated June 9, 2015, for complete information.

Dr. Pedras-Vasconcelos has indicated that the binding assay and the *in vitro* and cell-based neutralizing antibody assays are suitable to monitor immunogenicity to sebelipase alfa during enzyme replacement therapy for LAL deficiency.

Results from two clinical trials, an open-label, historically-controlled trial in infants with rapidly progressive disease (LAL-CL03) and a double-blind, placebo-controlled trial in pediatric and adult patients with LAL deficiency (LAL-CL02) were submitted in support of BLA 125561.

In Study LAL-CL03, 9 infants with rapidly progressive LAL deficiency (Wolman disease) were treated with sebelipase alfa weekly. The immunogenicity sampling in these patients was performed prior to dosing at prescreening, 2, 8, and 12 weeks, and every 6 months until 24 months, or at the time of early withdrawal. Two infants died during the first week of the study due to complications secondary to their underlying disease. These patients presented with fulminant symptoms of LAL deficiency at the time of clinical trial enrollment.

Seven of the 9 infants had at least one post-treatment anti-drug antibody (ADA) assessment. Of the 7 patients with immunogenicity data, 4 (57%) patients developed ADA during treatment with sebelipase alfa. Two of the 4 ADA-positive patients were determined to be positive for neutralizing antibodies (NAb) that inhibit *in vitro* enzyme activity and cellular uptake of the enzyme. At the time of initial ADA positivity, 3 patients were receiving a dosage of 1 mg/kg once weekly and 1 patient was receiving a dosage of 3 mg/kg once weekly. Three of the 4 ADA-positive patients had ADA titers monitored from the initiation of treatment, and developed measureable ADA titers within the first 2 months of exposure. One of the 4 ADA-positive patients developed persistent ADA titers. ADA titers decreased to undetectable levels in the remaining 3 patients while receiving continued treatment at a dosage of 3 mg/kg once weekly.

Hypersensitivity reactions occurred in all 4 of the ADA-positive patients, whereas they occurred in 1 of the 3 ADA-negative patients. None of the patients discontinued treatment. One patient experienced decreased growth velocity in a setting of neutralizing antibodies to sebelipase alfa.

Study LAL-CL02 included 66 pediatric and adult patients with LAL deficiency (cholesteryl ester storage disease [CESD]); 36 patient received sebelipase alfa 1 mg/kg IV every other week and 30 patients received placebo. Of the 36 patients who received sebelipase alfa, 35

patients continued treatment beyond Week 2 and had immunogenicity data available. Five (14%) of these 35 patients developed measurable ADA titers within the first 3 months of exposure. Two of the 5 ADA-positive patients had a measurable ADA titer at only one time point. In the 3 patients with measurable ADA titers at multiple time points, ADA titers decreased to undetectable levels during continued treatment. None of these patients tested positive for NAb during the 20-week double-blind treatment period.

Upon completion of the double-blind period, all patients received sebelipase alfa 1 mg/kg IV every other week in an open-label extension trial. One patient required dose escalation to 3 mg/kg once every other week during the extension period due to inadequate clinical response. Two patients developed *in vitro* neutralizing antibodies during the open-label extension trial after 20 weeks and 52 weeks of treatment with sebelipase alfa, respectively. There was no clear association between the development of ADA and hypersensitivity reactions or decreased efficacy in pediatric and adult patients treated with sebelipase alfa.

Dr. Pedras-Vasconcelos has not recommended PMCs or PMRs.

4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Pharmacology/Toxicology review by Dr. T. Chakraborti, dated June 8, 2015, for complete information. I have summarized Dr. Chakraborti's review findings below.

In a rat disease model of LAL deficiency that exhibits several abnormalities analogous to the human disease ("Yoshida" rat is a Donryu rat that contains a spontaneous 3' deletion mutation in the *LIPA* gene), sebelipase alfa administered intravenously at dosages up to 3 mg/kg once weekly showed improvements in several disease-related parameters, such as survival, body weight gain, organ weight reduction, reduction in cholesteryl esters and triglycerides in the liver and spleen, and reductions in serum transaminases lipids. In addition, study results supported a benefit of maintaining regular dosing of sebelipase alfa, as the animals showed a decline in growth velocity and loss of body weight following cessation of sebelipase alfa treatment.

Intravenous repeated dose toxicology studies were conducted in rats (4-week) and in Cynomolgus monkeys (4-week and 6-month). The No Observed Adverse Effect Levels (NOAELs) in 4-week intravenous toxicology studies in rats and Cynomolgus monkeys were 50 mg/kg/day in both species. The NOAEL in the 6-month intravenous toxicity study in Cynomolgus monkeys was 30 mg/kg/day. No significant organ toxicities were identified in these studies.

Sebelipase alfa at intravenous doses up to 60 mg/kg administered twice weekly was found to have no adverse effect on fertility and reproductive performance of male and female rats. In addition, animal reproductive studies conducted with sebelipase alfa showed no evidence of embryolethality, fetotoxicity, teratogenicity, or abnormal early embryonic development at

dosages up to 164 and 526 times the recommended human dosage of 1 mg/kg every other week (based on AUC) in rats and rabbits, respectively.

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

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Clinical Pharmacology review by Drs. J. Fang and S. Dorff, dated June 10, 2015, for complete information. The Clinical Pharmacology reviewers consider the information submitted in the BLA acceptable to support the approval of sebelipase alfa. I have summarized key review findings from the Clinical Pharmacology review below.

Two clinical trials, Study LAL-CL03 conducted in infants with rapidly progressive disease and Study LAL-CL02 conducted in pediatric and adult patients with LAL deficiency, contributed primarily to the clinical pharmacology assessment.

The Clinical Pharmacology reviewers indicated that it is not possible to evaluate the appropriateness of dosing regimens for patients with LAL deficiency from an exposure-response perspective, because the relevance of exposure-response based on systemic exposure of sebelipase alfa is not clear. In addition to having a very short plasma half-life of 6 minutes, the biological activity of sebelipase alfa is primarily driven by the exposure in the lysosomes of target tissue. At this time, the relationship between systemic exposure and concentration of sebelipase alfa in the lysosomes is unknown. As a result, the exposure-response relationships based on systemic exposure measures could only be considered supportive, and the selected dosing regimens were based primarily on efficacy and safety data. The reader is referred to Sections 7 and 8 of this document for a more detailed discussion of efficacy and safety data.

Evaluation of the proposed dosing regimens

Infants with rapidly progressive LAL deficiency (Wolman disease)

The proposed dosage of sebelipase alfa in infants with rapidly progressive LAL deficiency is 1 mg/kg once weekly initially, followed by escalation to 3 mg/kg once weekly in patients who do not achieve optimal clinical response.

The safety and efficacy of sebelipase alfa in infantile-onset LAL deficiency were evaluated in Study LAL-CL03, a multicenter, single-arm clinical study of sebelipase alfa in 9 infants with LAL deficiency who had growth failure or other evidence of rapidly progressive disease prior to 6 months of age. Due to the small number of enrolled patients and rapidly fatal clinical course, PK sampling was limited in this patient population. Timing of dose escalation differed across individuals and was prompted by suboptimal clinical response. Although the Applicant conducted a population PK analysis with the available data, the reviewers determined that the model did not fit the data satisfactorily and was deemed not suitable for simulating PK profiles or estimating PK parameters in infants. As a result, individual clinical data were reviewed to evaluate the effect of treatment and to inform dosing in infants.

In Study LAL-CL03, 8 of the 9 enrolled patients received 0.35 mg/kg once weekly as the starting dosage (one patient received 0.20 mg/kg prior to the 0.35 mg/kg dose). Two patients died after receiving a single dose of 0.35 mg/kg. After receiving 0.35 mg/kg once weekly for 2 weeks, 7 surviving patients had their dosage escalated to 1 mg/kg once weekly and remained at this dosage for varying duration depending on clinical response. Due to suboptimal clinical response (e.g., inadequate weight gain, organomegaly), 6 remaining surviving patients were dose-escalated to 3 mg/kg once weekly. In one patient, the dosage was escalated to 5 mg/kg once weekly at Week 88 due to decreased growth velocity.

Of the 9 sebelipase alfa-treated infants, 6 (67%) patients survived beyond 12 months of age, compared to 0 of 21 patients in the historical cohort (LAL-1-NH01 natural history study), all of whom died by 8 months of age. Since all surviving patients received 1 mg/kg once weekly and benefited from dose-escalation to 3 mg/kg when there was inadequate clinical response, the reviewers have concluded that the Applicant's proposed dosing regimen is acceptable. I agree with their assessment as it is important to optimize the dose as quickly as possible in this vulnerable patient population with rapidly progressive disease. It should also be noted that the reviewers have not identified safety concerns with initiating sebelipase alfa treatment at 1 mg/kg once weekly (as opposed to initiating with 0.35 mg/kg once weekly as done in Study LAL-CL03).

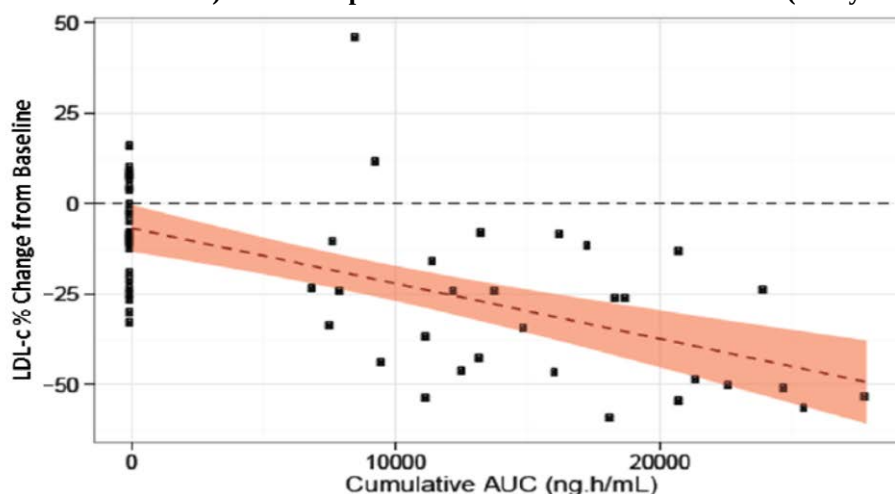
Pediatric and adult patients with LAL deficiency (cholesteryl ester storage disease [CESD])

The proposed dosage of sebelipase alfa in pediatric and adult patients with LAL deficiency is 1 mg/kg once every other week.

The safety and efficacy of sebelipase alfa were assessed in 66 pediatric and adult patients with LAL deficiency (aged 4 to 58 years) in Study LAL-CL02, a multicenter, double-blind, placebo-controlled trial. In Study LAL-CL02, patients were randomized to receive sebelipase alfa at a dosage of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks. At the completion of the 20-week double-blind period of the trial, a statistically significant improvement from baseline in LDL-c was observed in the sebelipase alfa-treated group as compared to the placebo group ($-28 \pm 22\%$ vs. $-6 \pm 13\%$; $p < 0.0001$).

The Applicant evaluated the exposure-response relationship using cumulative AUC from baseline to Week 20 as the exposure variable and the primary efficacy endpoint of percent change from baseline in LDL-c at Week 20 as the response variable. As shown in Figure 1, the percent change from baseline in LDL-c increased with increasing exposure. The reviewers stated that a similar exposure-response relationship was not evident for any of the other efficacy endpoints (HDL-c, cholesterol, triglycerides, ALT, and liver fat content).

Figure 1: Exposure-response relationship for the primary efficacy endpoint (% change from baseline in %LDL-c) with sebelipase alfa cumulative AUC at Week 20 (Study LAL-CL02)



The dashed red line represents a least squares linear regression, the shaded regions are the 95% CIs of the regression lines, and the dashed grey line indicates no change from baseline.

Source: Clinical Pharmacology review by Dr. J. Fang, dated June 10, 2015; Figure 1 in Section 2.4.1 (Also included in the Applicant's updated clinical pharmacology response 2 to the FDA's Information Request dated April 16, 2015; Figure 11).

Taken together, the reviewers have concluded that systemic exposures achieved by Week 20 are adequate to achieve clinical efficacy and, therefore, the Applicant's proposed dosing regimen of 1 mg/kg once every other week is acceptable for pediatric and adult patients with LAL deficiency.

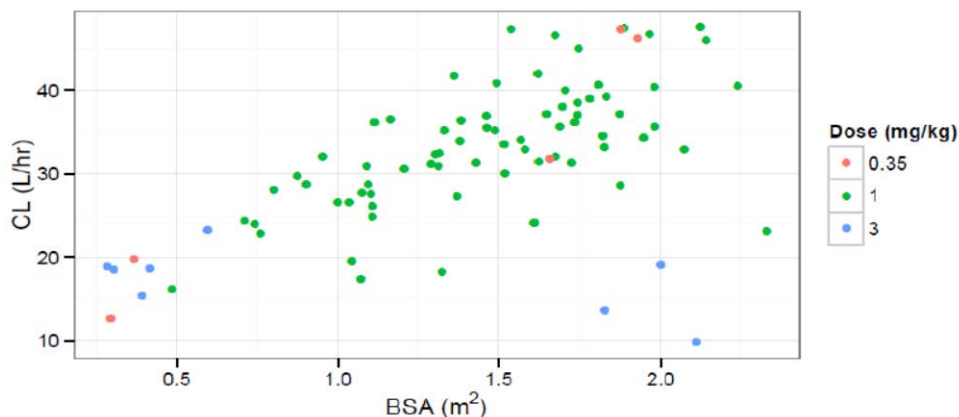
Pharmacokinetics

In adult patients, sebelipase alfa serum concentration rose quickly within the first hour after initiating the infusion; C_{max} reached close to or at the end of infusion. Upon completion of the infusion, the systemic concentration of sebelipase alfa decreased rapidly with a median $t_{1/2}$ ranging from 0.11 to 0.26 h at 1 mg/kg dose and 0.11 to 0.21 h at 3 mg/kg dose.

The Clinical Pharmacology reviewers have determined that the exposure of sebelipase alfa in serum increased in a dose proportional manner between 0.35 mg/kg and 1 mg/kg, but in a greater than dose-proportional manner between the 1 and 3 mg/kg doses following a single dose and multiple doses of sebelipase alfa. A 3-fold increase in dose from 1 mg/kg to 3 mg/kg resulted in approximately 10- to 15-fold increases in exposure, including the area under the concentration-time curve from time zero to last quantifiable measurement (AUC_{0-last}), AUC from time zero to infinity (AUC_{0-inf}), and maximum concentration (C_{max}). The PK parameters for sebelipase alfa were comparable following the administration of a single and multiple doses, and there was no accumulation of sebelipase alfa with repeated dosing.

Body surface area was a significant covariate in the population PK analysis of data in children (4-17 years old) and in adults. As shown in Figure 2, the sebelipase alfa clearance increased with increasing body surface area, supporting a weight-based dosing regimen.

Figure 2: Relationship between sebelipase alfa clearance (CL) and body surface area (BSA)



Source: Clinical Pharmacology review by Dr. J. Fang, dated June 10, 2015;
Figure 4 in Section 2.6.1.

Table 1 summarizes the pharmacokinetic parameters of sebelipase alfa at the proposed marketing dosage of 1 mg/kg once every other week. Using a population pharmacokinetic model, sebelipase alfa pharmacokinetic parameters at Week 22 were estimated for 65 pediatric and adult patients who received intravenous infusions of sebelipase alfa at 1 mg/kg in Study LAL-CL02; 24 patients were 4 to 11 years old, 23 were 12 to 17 years old, and 18 were adults. The pharmacokinetic profiles of sebelipase alfa were similar between adolescents and adults. The T_{max} and $T_{1/2}$ were similar across all age groups. This information is included in Section 12 (Clinical Pharmacology) of the labeling.

Table 1: Mean (SD) PK parameters at Week 22 in pediatric and adult patients with LAL deficiency receiving 1 mg/kg once every other week

Parameter	4-11 years old	12-17 years old	≥18 years old
	N=24	N=23	N=18
AUC (ng·hr/mL)	942 (388)	1454 (699)	1861 (599)
C_{max} (ng/mL)	490 (205)	784 (480)	957 (303)
T_{max} (hr)	1.3 (0.6)	1.1 (0.3)	1.3 (0.6)
CL (L/hr)	31.1 (7.1)	37.4 (12.4)	38.2 (12.5)
V_c (L)	3.6 (3.0)	5.4 (2.4)	5.3 (1.6)
$T_{1/2}$ (min)	5.4 (4.3)	6.6 (3.7)	6.6 (3.7)

AUC, area under the plasma concentration time curve; C_{max} , maximum concentration; T_{max} , time to maximum concentration; CL, clearance; V_c , central volume of distribution, $T_{1/2}$, half-life.

Source: Adapted from Clinical Pharmacology review by Dr. J. Fang, dated June 10, 2015; Table 8 in Section 2.6.1 (Also, the Applicant's response to Clinical Pharmacology IR dated May 7, 2015).

Due to very limited PK data in infants, it was not possible to characterize pharmacokinetics of sebelipase alfa in infants.

Impact of LIPA genotype on the PK, efficacy and safety of sebelipase alfa

Lysosomal acid lipase deficiency is caused by mutations in the *LIPA* gene. *LIPA* genotype was assessed in 81/84 (96%) of patients in the sebelipase alfa clinical development program. Across clinical studies, 65/84 (77%) of patients were homozygous or heterozygous for a splice-site mutation (c.894G>A) affecting exon 8. This mutation is associated with LAL deficiency presenting in pediatric and adult patients with LAL deficiency (CESD), but not in infants (no single mutation was present predominantly in infants).

No difference by c.894G>A genotype was observed for PK or efficacy in Study LAL-CL02. Anti-drug antibodies (ADAs) developed in patients from all studies across a variety of *LIPA* mutation combinations, and hypersensitivity reactions were observed in patients with and without ADA positivity. Therefore, the reviewers have concluded that specific mutations or the functional impact of the disease causing mutations are not likely to influence exposure or response to sebelipase alfa.

The Clinical Pharmacology reviewers have not recommended PMCs or PMRs.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application, because sebelipase alfa is not intended as an antimicrobial product.

7. Clinical/Statistical- Efficacy

The reader is referred to the Statistical review by Mr. B. Vali, dated June 12, 2015. Clinical reviews were performed by Drs. L. Weintraub and J. Tomaino. The statistical and clinical reviewers recommend approval of BLA 125561, and I agree with their recommendation. Below, I have summarized the key findings from their reviews.

The Applicant submitted the results from two clinical trials, an open-label, single-arm trial (LAL-CL03) in infants with rapidly progressive disease (Wolman disease) and a randomized, double-blind, placebo-controlled trial (LAL-CL02) in pediatric and adult patients with LAL deficiency (CESD), to support the efficacy of sebelipase alfa in patients with LAL deficiency. Dr. Weintraub reviewed Study LAL-CL03 and Dr. Tomaino reviewed Study LAL-CL02.

Patients with rapidly progressive LAL deficiency presenting within the first 6 months of life (Study LAL-CL03)

Study Design

Study LAL-CL03 was a multinational (9 countries), multicenter (12 clinical sites), open-label, single-arm trial conducted in 9 infants presenting with rapidly progressive LAL deficiency. A historical control group from a retrospective natural history study conducted in Wolman disease (LAL-1-NH01) was used as a comparator. The reviewers have determined that the use

of a historical control group from the LAL-1-NH01 study is reasonable in this setting, since the course of untreated Wolman disease has been well characterized with a predictable clinical outcome (i.e., fatal within the first 8 months of life), the use of an objective primary endpoint with the outcome on treatment being markedly different from that of the historical control (i.e., survival vs. no survival), and patients in the natural history study closely resembling the trial group in all relevant baseline and observational variables.

Patient Population/Demographic and Baseline Characteristics

Study LAL-CL03 enrolled 9 infants presenting with growth failure or other evidence of rapidly progressive disease prior to 6 month of age. The age at symptom onset was 0 to 5 months (mean $\pm$ SD of 1.5 ± 1.6 months), and the age range at entry was 1 to 6 months. Twenty-one Wolman disease patients with similar disease characteristics and age at symptom onset (range of 0 to 3 months with a mean $\pm$ SD of 1.4 ± 1.1 months) were extracted from the LAL-1-NH01 study to serve as the historical control group.

Treatment

Eight of 9 enrolled patients received sebelipase alfa 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. One patient received 0.20 mg/kg prior to receiving the 0.35 mg/kg dose. Two patients died after receiving a single dose of 0.35 mg/kg. These patients presented with fulminant symptoms of LAL deficiency at the time of clinical trial enrollment. Seven remaining patients had their dosage escalated to 1 mg/kg once weekly and remained at this dosage for varying duration depending on clinical response. Due to suboptimal clinical response (e.g., inadequate weight gain, organomegaly), doses in all 6 surviving patients were escalated to 3 mg/kg once weekly, between 4 and 88 weeks (median 11 weeks) after starting treatment at 1 mg/kg. In one patient, the dosage was further escalated to 5 mg/kg once weekly at Week 88. This patient also had positive neutralizing anti-drug antibodies to sebelipase alfa.

Analysis of Primary Endpoint

The primary endpoint was time to death from birth up to Month 12. Efficacy of sebelipase alfa was assessed by comparing the survival of 9 sebelipase alfa-treated patients at 12 months of age with an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Of the 9 sebelipase alfa-treated infants, 6 (67%; 95% CI [30%, 93%]) patients survived beyond 12 months of age, compared to 0 (0%; 95% CI [0%, 16%]) of 21 patients in the historical cohort (LAL-1-NH01 study), all of whom died by 8 months of age. Table 2, reproduced from the Statistical Review, summarizes the primary efficacy analysis.

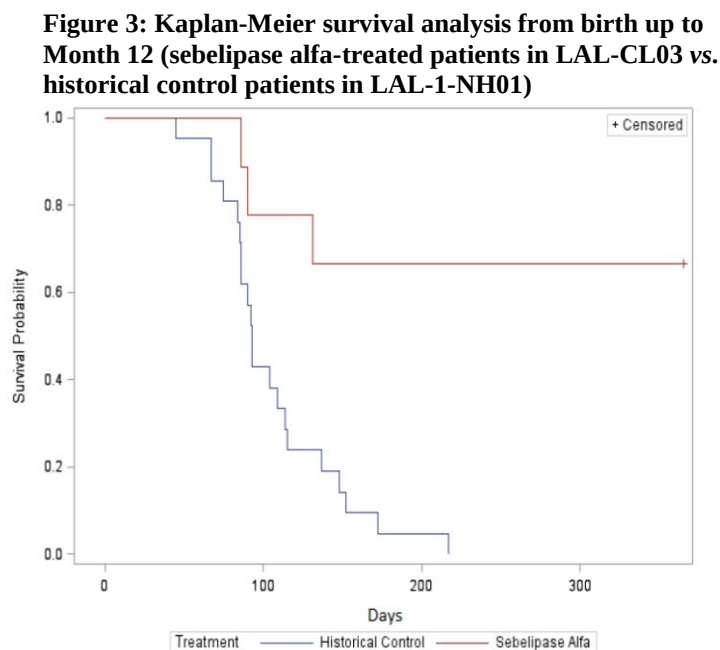
Table 2: Time to death from birth up to Month 12 in sebelipase alfa-treated patients in LAL-CL03 compared to historical control patients in LAL-1-NH01

	Sebelipase Alfa (N = 9)	Historical Control (N = 21)	Treatment Difference (Sebelipase Alfa / Historical Control)
Alive at Month 12 – n (%)	6 (66.7%)	0 (0.0%)	
Corresponding 95% CI [1]	(29.9%, 92.5%)	(0.0%, 16.1%)	
Time to Death from Birth (in Days)			
n	9	21	
Mean (SD)	277.6 (132.05)	106.2 (39.95)	
Median	365.3	93.0	
Min, Max	86, 365.3*	45, 217	
Hazard Ratio [2]			0.141
Corresponding 95% CI [2]			(0.040, 0.496)
Log-Rank test p-value [2]			0.0006

* denotes censoring; [1]: using the Clopper-Pearson method; [2]: Applicant's pre-specified analysis

Source: Statistical review by Mr. B. Vali, dated June 12, 2015; Table 4 in Section 3.2.1.4.

Figure 3, also reproduced from the Statistical review, illustrates the Kaplan-Meier survival analysis from birth up to Month 12 in sebelipase-alfa treated patients in Study LAL-CL03, compared with historical control patients in LAL-1-NH01.



Source: Statistical review by Mr. B. Vali, dated June 12, 2015;
Figure 1 in Section 3.2.1.4.

Based on above analyses, the Statistical reviewer concluded that sebelipase alfa treatment demonstrated a superior outcome with respect to survival, i.e., time to death from birth up to Month 12, compared to an untreated historical control group. I agree with his assessment. In

addition, it is reassuring that the median age of the 6 surviving sebelipase alfa-treated patients was well over 12 months (18 months; range 12 to 42 months).

Growth Assessment

In 3 of the 5 surviving patients who initially presented with growth failure, the weight-for-age z-scores improved following treatment with sebelipase alfa 1 mg/kg once weekly, and all 6 surviving patients demonstrated improved weight-for-age z-scores following dose escalation to 3 mg/kg once weekly.

Based on compelling survival data and supportive growth data, I agree with the reviewers that submitted data are adequate to support the efficacy of sebelipase alfa in infants with rapidly progressive LAL deficiency presenting within the first 6 months of life.

Pediatric and Adult Patients with LAL deficiency (Study LAL-CL02)

Study Design

Study LAL-CL02 was a multinational (17 countries), multicenter (55 clinical sites), randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of sebelipase alfa in 66 pediatric and adult patients with LAL deficiency. Patients were randomized to receive sebelipase alfa at a dosage of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. No dose modifications were permitted during the double-blind treatment period.

Patient Population/Demographic and Baseline Characteristics

Study LAL-CL02 enrolled 66 pediatric and adult patients with LAL deficiency, aged 5 to 58 years (71% were pediatric patients less than 18 years old). Thirty-three (50%) patients were males. Patients were stratified into one of three groups: (1) age at randomization (<12 years vs. ≥12 years), (2) average screening ALT level (<3x upper limit of normal [ULN] vs. ≥3x ULN), and (3) use of lipid lowering medications (yes vs. no).

The mean age of the patient population was 16 ± 11 years (median: 13 years, range 4-58 years). Of the 66 patients, 24 (36%) patients were < 12 years old and 42 (64%) patients were ≥ 12 years old. Of the 42 patients who were ≥ 12 years of age at randomization, 23 patients were between 12 and < 18 years and 19 patients were ≥ 18 years. The reviewers did not identify imbalance between the treatment groups with regard to demographic and baseline characteristics that could have affected the outcome of efficacy analyses.

Only one patient in the sebelipase alfa treatment group discontinued from the trial due to an adverse reaction; the remaining 65 (98%) patients completed 20 weeks of double-blind treatment period.

Sixty-two of the 66 (94%) patients had a baseline LDL-cholesterol (LDL-c) of 130 mg/dL or greater at study entry. The majority of patients (58%) had LDL-c above 190 mg/dL at study entry, and 24% of patients with LDL-c above 190 mg/dL remained on lipid lowering medications.

It should be noted that a central laboratory was utilized to assess all laboratory parameters.

Analysis of Primary Endpoint

The primary objective of this trial was to demonstrate normalization of ALT, supported by improvements in other biochemical and clinical parameters (i.e., LDL-c, non-HDL-c, TG, AST, HDL-c, liver fat content, and liver volume). However, the Applicant's proposed primary efficacy endpoint, normalization of ALT, neither directly measures clinical benefit of treatment (i.e., how a patient feels, functions, or survives) nor represents a surrogate endpoint reasonably likely to predict clinical benefit in patients with late-onset LAL deficiency (i.e., pediatric and adult patients with CESD). While elevated serum transaminases usually represent liver injury, ALT is not on the causal pathway of disease and there are currently no data to support that ALT levels reflect injuries due to accumulation of cholesteryl esters and triglycerides in the liver of patients with CESD. Therefore, normalization of ALT does not reliably represent a clinical benefit (b) (4) in this patient population. These concerns were communicated to the Applicant on multiple occasions during pre-submission meetings (see regulatory history in Section 2) and during the review cycle.

Since ALT normalization is not appropriate to serve as the basis to establish efficacy in the CESD patient population, the clinical review team determined that the first-ranked secondary endpoint, LDL-c, would be the most suitable endpoint to assess efficacy in this patient population. LDL-c is included in the causal pathway of LAL deficiency, as LDL-c is made up in part by cholesteryl esters and triglycerides that accumulate in the lysosome when LAL is deficient, thereby contributing to disease manifestations seen in patients with CESD. In addition, elevation of LDL-c is a well-established risk factor for coronary heart disease, and hyperlipidemia and accelerated atherosclerosis are known complications of LAL deficiency. The Statistical reviewer stated that, due to the Applicant's pre-specified step-down/closed sequential testing procedure in tandem with successful hypothesis testing for the pre-specified primary endpoint of ALT normalization at Week 20 ($11 \pm 31\%$ in sebelipase-alfa treated patients vs. $2 \pm 7\%$ in placebo-treated patients; mean difference and 95% CI: 24%, [6%, 41%]; $p=0.03$), formal hypothesis testing of LDL-c was ensured for labeling purposes.

Treatment with sebelipase alfa resulted in a greater reduction in the percent change from baseline to Week 20 in LDL-c, compared to placebo (mean difference and 95% CI: -22%, [-33%, -15%]; $p<0.0001$). Patients treated with sebelipase alfa had a mean $\pm$ SD reduction from baseline in LDL-c of $28 \pm 22\%$, compared to $6 \pm 13\%$ in placebo-treated patients. The Statistical reviewer stated that additional sensitivity analyses he conducted did not change study conclusions.

At the completion of the 20-week double-blind period of the trial, LDL-c level of less than 130 mg/dL (range that reduces the risk of developing coronary heart disease)⁷ was achieved in 13 of 32 (41%; 95% CI: [24%, 58%]) sebelipase alfa-treated patients and in only 2 of 30 (7%; 95% CI: [0%, 16%]) placebo-treated patients with a baseline LDL-c level of 130 mg/dL or greater.

⁷ Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-97.

Use of lipid lowering medication use:

At baseline, 26 (39%) of 66 patients were receiving lipid lowering medication and the remaining 40 (61%) patients were not. The dose of lipid lowering medication remained unchanged during the double-blind period. It should be noted that the mean baseline LDL-c was abnormal in patients despite treatment with lipid lowering medication: the baseline mean LDL-c was 174 mg/dL in patients receiving lipid lowering medication and 230 mg/dL in patients not receiving lipid lowering medication. As shown in Table 3, the Clinical reviewer's exploratory analysis demonstrated that both treatment groups experienced reductions in LDL-c from baseline; however, the combination of lipid lowering medication with sebelipase alfa appears to have a numerically greater reduction in LDL-c compared to treatment with sebelipase alfa alone.

Table 3: Mean percent change from baseline in LDL-c by treatment group and baseline use of lipid lowering medications

% Change from Baseline LDL-c	LLM		No LLM		Total/Combined	
	SA (n = 15)	Placebo (n = 11)	SA (n = 21)	Placebo (n = 19)	SA (n = 36)	Placebo (n = 30)
Mean ± SD (%)	-37 ± 16	-10 ± 15	-23 ± 25	-4 ± 12	-28 ± 22	-6 ± 13
Difference	-27		-18		-22	
95% CI*	-39, -15		-30, -7		-31, -13	

LLM, lipid lowering medication; SA, sebelipase alfa

*95% CI and Total/Combined were calculated by the FDA statistical reviewer.

Source: Clinical review by Dr. J. Tomaino, dated June 8, 2015; Table 11 in Section 6.1.5.

Of the patients with abnormal LDL-c (> 130 mg/dL) at baseline, 13 (41%) of 32 patients in the sebelipase alfa group achieved an LDL-c level of < 130 mg/dL as compared to only 2 (7%) of 30 patients in the placebo group. While these findings are based on a small number of patients and exploratory in nature, treatment with sebelipase alfa appears to have the ability to lower LDL-c beyond what is achieved with lipid lowering therapy.

Analysis of Secondary Endpoints

The secondary endpoints evaluated by the Applicant include (in pre-specified order):

- 1) Decrease in LDL-c (the review team determined that this endpoint is most suitable as the primary endpoint)
- 2) Decrease in non- high density lipoprotein (non-HDL-c)
- 3) Normalization of aspartate aminotransferase (AST)
- 4) Decrease in triglyceride (TG)
- 5) Increase in high-density lipoprotein cholesterol (HDL-c)
- 6) Decrease in liver fat content (%) using multi-echo gradient-echo proton density fat fraction (MEGE PDFF) MRI (in a subset of patients for whom imaging was performed)
- 7) Improvement in liver histopathology (in a subset of patients for whom biopsy was performed)
- 8) Decrease in liver volume, as measured by MRI and reported in multiples of normal (in a subset of patients for whom imaging was performed)

In order to control the overall study-wise type I error rate, the Applicant pre-specified a step-down/closed sequential testing procedure to adjust for the multiple comparisons on the

efficacy endpoints, including the secondary endpoints presented in the above order. Starting with the primary endpoint, the Applicant pre-specified that the step-down could only be carried to the next endpoint, if and only if the current endpoint/step was found to be statistically significant in the comparison of sebelipase alfa to placebo (i.e., p-value less than 0.05). All secondary endpoints up to percent decrease in liver fat content resulted in statistically significant results (Table 4). However, there was no difference in the proportion of patients achieving improvement in liver histopathology at Week 20 between sebelipase alfa and placebo groups. Due to the negative formal hypothesis test result for this endpoint, hypothesis testing for the subsequent endpoint (i.e., decrease in liver volume) was considered exploratory.

Table 4: Change from baseline to Week 20 in secondary efficacy endpoints in pediatric and adult patients with LAL deficiency (LAL-CL02)

Efficacy Endpoint	Sebelipase alfa (n=36)	Placebo (n=30)	Statistically significant in fixed sequence test
LDL-c % change from baseline n Mean ± SD	36 -28 ± 22	30 -6 ± 13	Yes
Mean difference (95% CI) p-value [†]	-22 (-33, -15) < 0.0001		
non-HDL-c % change from baseline n Mean ± SD	36 -28 ± 19	30 -7 ± 11	Yes
Mean difference (95% CI) p-value [†]	-21 (-30, -15) < 0.0001		
AST normalization n Yes, n (%)	36 15 (42%)	29 1 (3%)	Yes
Difference p-value [*]	39% 0.0003		
Triglyceride % change from baseline n Mean ± SD	36 -25 ± 30	30 -11 ± 29	Yes
Mean difference (95% CI) p-value [†]	-14 (-28, -1) 0.0375		
HDL-c % change from baseline n Mean ± SD	36 19 ± 16	30 -1 ± 12	Yes
Mean difference (95% CI) p-value [†]	20 (12, 26) < 0.0001		
Liver fat content % change from baseline n Mean ± SD	32 -32 ± 27	25 -4 ± 16	Yes
Mean difference (95% CI) p-value [†]	-28 (-41, 19) < 0.0001		
Improvement in liver histopathology n Yes, n (%)	16 10 (63)	10 4 (40)	No
Difference p-value [*]	23% 0.42		
Liver volume % change from baseline (MN) n Mean ± SD	33 -10 ± 11	27 -3 ± 10	No
Difference (95% CI) p-value [†]	-8 (-13, -3) 0.004		

^{*}p-value calculated using Fisher's exact test; [†]p-value calculated using Wilcoxon rank sum test; MN, multiples of normal

Source: Clinical review by Dr. J. Tomaino, dated June 8, 2015; Tables 10, 13, 14, 15, 16, and 17, and Figure 9 in Section 6.1.5.

The Clinical reviewer for Study LAL-CL02, Dr. J. Tomaino, asserts that similar to ALT, AST neither directly measures clinical benefit of treatment nor represents a surrogate endpoint reasonably likely to predict clinical benefit in patients with CESD. (b) (4)

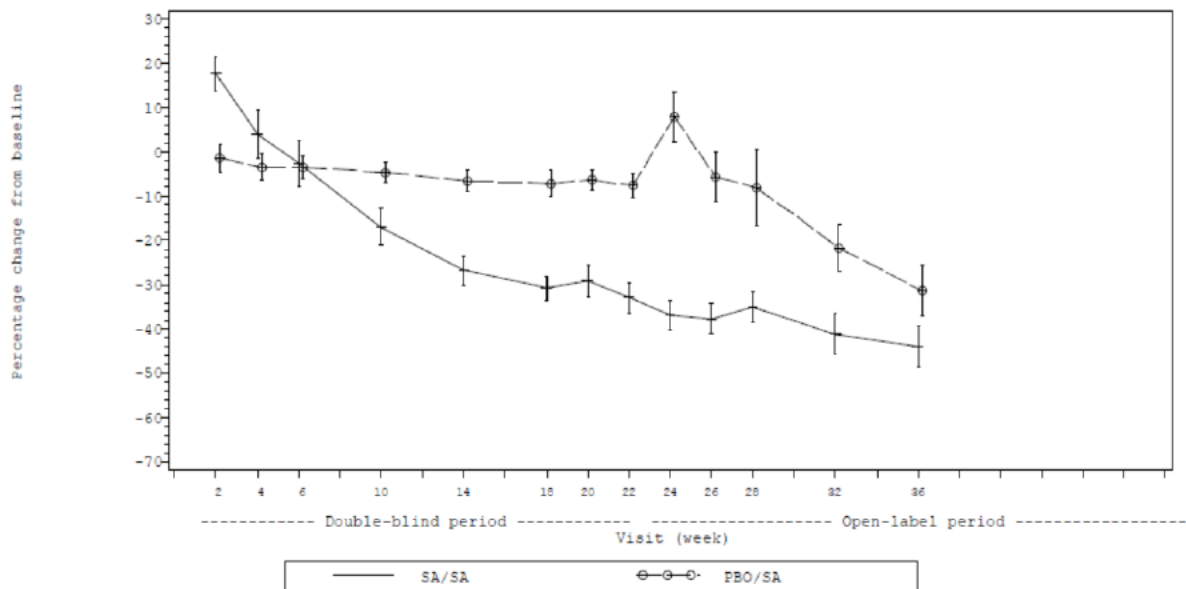
(b) (4)

although a decrease in liver fat content achieved statistical significance, Dr. Tomaino indicated that there are currently no data available to support that a reduction in liver fat correlates with improved long-term liver disease outcomes in patients with CESD. It should also be noted that this endpoint was evaluated only in a subset of patients who underwent imaging study. Although the percent change from baseline in liver fat content was greater in the sebelipase alfa-treated group compared to placebo, the actual amount of decrease in fat content from baseline was not striking. For example, the mean liver fat content decreased from $9 \pm 4\%$ at baseline to $5 \pm 2\%$ after 20 weeks of sebelipase alfa treatment. (b) (4)

Open-label Extension

Upon completion of the 20-week double-blind treatment period, pediatric and adult patients with LAL deficiency who participated in the randomized, placebo-controlled trial were eligible to continue sebelipase alfa treatment in the open-label extension period. Regardless of their original randomized treatment assignment, all patients in the extension period received open-label sebelipase alfa treatment at a dosage of 1 mg/kg once every other week. Dose escalation to 3 mg/kg once every other week was permitted during the extension period in patients who have inadequate clinical response. The double-blind treatment period ended on May 30, 2014, and the open-label treatment period is currently ongoing. As shown in Figure 4, patients treated with sebelipase alfa for up to 36 weeks demonstrated improvements in LDL-c levels. Similar improvements were also observed for HDL-c and ALT.

Figure 4: Mean percent change in lipid levels over time in Study LAL-CL02 and extension



Treatment sequence: SA/SA: Sebelipase Alfa/Sebelipase Alfa, PBO/SA: Placebo/Sebelipase Alfa;
 Baseline: Last measurement prior to first study drug infusion of sebelipase alfa. In case of multiple pre-treatment measurements, the average of the last (up to 3) measurements within 45 days;
 Visits for a treatment sequence are presented as long as at least 5 subjects for that treatment sequence are available;

Source: Applicant's BLA 125561 submission, Study LAL-CL02 Clinical Study Report; Figure 24 in Section 10.4.1.

Despite improvements in lipid parameters, the effect of sebelipase alfa on cardiovascular morbidity and mortality has not been established. In addition, the trial was not sufficient in duration to assess a clinically meaningful change in the underlying liver disease (e.g., progression to end stage liver disease, receipt of liver transplantation). In order to evaluate the long-term clinical benefit of sebelipase alfa on cardiovascular and liver outcomes, the Clinical reviewers have recommended the following PMC study:

Evaluate the long-term, prospective clinical outcomes of treatment with sebelipase alfa in adult and pediatric patients with LAL deficiency, including but not limited to progression of liver and cardiovascular diseases and changes in anthropometric assessments (i.e., length/height z-scores, and weight z-scores). At a minimum, liver assessments will include results of liver biopsies and imaging studies, changes in liver synthetic function, evidence for clinical progression to end stage liver disease (e.g., assessed by the Model for End-Stage Liver Disease [MELD] score), receipt of liver transplantation, and fatal outcomes. Cardiovascular assessments will include incidence rates of non-fatal stroke, myocardial infarction, and cardiovascular death. Additional evaluations will include dosing regimens administered and reasons for any dose modifications. This study will also collect data on the occurrence of any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Eligible patients will be enrolled over an initial 3-year period and followed for a minimum of 10 years from the time of enrollment or until death, whichever comes first. This study may be conducted as a separate study or as a sub-study within the Lysosomal Acid Lipase registry.

8. Safety

The safety review was conducted by Drs. L. Weintraub and J. Tomaino. Below, I have summarized their safety findings from the two clinical trials that were submitted to support marketing approval of sebelipase alfa (Study LAL-CL03 in infants with rapidly progressive disease and Study LAL-CL02 in pediatric and adult patients with LAL deficiency). Dr. Weintraub reviewed Study LAL-CL03 and Dr. Tomaino reviewed Study LAL-CL02.

In Study LAL-CL03, 9 infants with rapidly progressive LAL deficiency received sebelipase alfa for up to 165 weeks at escalating doses ranging from 0.35 mg/kg and 5 mg/kg once weekly. Table 5 summarizes the most common adverse reactions that occurred in >30% of infants treated with sebelipase alfa in Study LAL-CL03. This information is included in Section 6 (Adverse Reactions) of the labeling.

Table 5: Most common adverse reactions (>30%) following sebelipase alfa treatment in infants with rapidly progressive LAL deficiency

Adverse Reaction	Sebelipase alfa N=9
	n (%)
Diarrhea	6 (67)
Vomiting	6 (67)
Fever	5 (56)
Rhinitis	5 (56)
Anemia	4 (44)
Cough	3 (33)
Nasopharyngitis	3 (33)
Urticaria	3 (33)

Other less commonly reported adverse reactions included hypotonia, decreased oxygen saturation, retching, sneezing, and tachycardia.

In Study LAL-CL02, 66 pediatric and adult patients with LAL deficiency, ages 4 to 58 years old, received sebelipase alfa 1 mg/kg once every other week up to 36 weeks. Table 6 summarizes the most common adverse reactions that occurred in $\geq 8\%$ of pediatric and adult patients receiving KANUMA at a dosage of 1 mg/kg once every other week during the 20-week double-blind treatment period. All of these adverse reactions occurred at a higher incidence than in patients receiving placebo.

Table 6: Most common adverse reactions ($\geq 8\%$ or ≥ 3 patients) following sebelipase alfa treatment in pediatric and adult patients with LAL deficiency

Adverse Reactions	Sebelipase alfa N = 36	Placebo N = 30
	n (%)	n (%)
Headache	10 (28)	6 (20)
Fever	9 (25)	7 (23)
Oropharyngeal pain	6 (17)	1 (3)
Nasopharyngitis	4 (11)	3 (10)
Asthenia	3 (8)	1 (3)
Constipation	3 (8)	1 (3)
Nausea	3 (8)	2 (7)

Source: Adapted from Clinical review by Dr. J. Tomaino, dated June 8, 2015; Table 29 in Section 7.4.1.

Other less common adverse reactions (6% or 2 patients) reported in pediatric and adult patients who received sebelipase alfa included anxiety, arthralgia, chest pain, gastritis, rhinorrhea, sinusitis, and syncope.

It should also be noted that increases in circulating LDL-cholesterol (LDL-c) and triglycerides above pre-treatment values were observed in 29 of 36 (81%) and 21 of 36 (58%) patients, respectively, at 2 to 4 weeks following initiation of sebelipase alfa. The maximum mean

percentage increase was 18% for LDL-c at Week 2 and 5% for triglycerides at Week 4. These increases generally improved from pre-treatment values within 8 weeks of sebelipase alfa treatment. The observed transient increases in LDL-c and triglycerides upon treatment initiation are thought to be due to mobilization of accumulated lysosomal lipids.

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylaxis, remain the most common and concerning adverse reactions associated with enzyme replacement therapies. The safety population to assess the incidence of hypersensitivity reactions, including anaphylaxis, included 106 patients who participated in completed and ongoing clinical trials.⁸

Anaphylaxis occurred in 3 (3 %) of 106 patients with LAL deficiency treated with sebelipase alfa during clinical trials. These patients experienced reactions during infusion with signs and symptoms including chest discomfort, conjunctival injection, dyspnea, generalized and itchy rash, hyperemia, swelling of eyelids, rhinorrhea, severe respiratory distress, tachycardia, tachypnea, and urticaria. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after treatment initiation.

Hypersensitivity reactions were reported in 21 (20%) of 106 sebelipase alfa-treated patients, including 9 (64%) of 14 infants and 12 (13%) of 92 pediatric and adult patients. The majority of hypersensitivity reactions occurred during or within 4 hours of the completion of the infusion. Common symptoms of hypersensitivity reactions (occurring in ≥ 2 patients) included abdominal pain, agitation, fever, chills, diarrhea, eczema, edema, hypertension, irritability, laryngeal edema, nausea, pallor, pruritus, rash, and vomiting.

Hypersensitivity reactions including anaphylaxis represent most important adverse reactions associated with sebelipase alfa treatment, and these are adequately described in the Warnings and Precautions section of the labeling. I agree with the reviewers that no concerning safety findings were identified to preclude approval of this application.

It is important to also note that sebelipase alfa is produced in the egg whites of genetically engineered chickens. Because patients with a known history of egg allergies were excluded from the clinical trials, it was not possible to assess whether patients with a history of egg allergies would have a different safety outcome when treated with sebelipase alfa. Hence, the labeling will communicate that the risks and benefits of treatment with sebelipase alfa should be considered in patients with known systemic hypersensitivity reactions to eggs or egg products.

The Clinical reviewers have not recommended safety-related PMRs.

⁸ 9 patients from LAL-CL03 (single-arm, open-label dose escalation trial in Wolman disease patients ≤ 24 months of age), 66 patients from LAL-CL02 (randomized, double-blind, placebo-controlled trial and its open-label extension trial in CESD patients ≥ 4 years of age), 9 patients from LAL-CL01/04 (single-arm, open-label dose escalation trial and its extension in CESD patients ≥ 18 and ≤ 65 years of age), 17 patients from LAL-CL06 (single-arm, open-label trial for LAL deficiency patients > 8 months of age who do not meet inclusion criteria for other trials, and 5 patients from LAL-CL08 (single-arm, open-label trial in infants with Wolman disease < 8 months of age)

Additional Safety Discussion

Role of immune tolerance induction

Published data support that patients who develop highly sustained antibody titers may be at risk of attenuated therapeutic response to enzyme replacement therapy,^{9,10} but are able to achieve immune tolerance through immune tolerance induction therapy.¹¹ Immune tolerance induction (using one or more immunomodulators) is usually implemented before or concomitant with onset of enzyme replacement therapy, with the goal of reducing antibody response to the drug antigen.

Seven of the 9 infants with rapidly progressive disease had at least one post-treatment anti-drug antibody (ADA) assessment, and 4 (57%) of these 7 patients developed ADA during treatment with sebelipase alfa. Two of the 4 ADA-positive patients were found to have positive neutralizing antibodies that inhibit *in vitro* enzyme activity and cellular uptake of the enzyme. However, only one of the 4 ADA-positive patients had persistent ADA titers, and ADA titers decreased to undetectable levels in the remaining 3 patients during continued treatment. One patient experienced decreased growth velocity in a setting of neutralizing antibodies to sebelipase alfa. However, based on limited data, no generalizable conclusion can be made regarding the development of ADA and decreased efficacy in this patient population. In addition, patients presenting with LAL deficiency during early infancy are particularly vulnerable, often presenting with multisystem failure and rapidly progressing to death. Based on disease characteristics and available clinical trial data, I believe that the known risk of infection associated with immune tolerance induction outweighs the potential benefit in this vulnerable patient population to support recommending immune tolerance induction.

Five of the 35 (14%) sebelipase alfa-treated pediatric and adult patients who completed the 20-week double-blind period of study treatment developed ADA. Two of the 5 ADA-positive patients had a measurable ADA titer at only one time point. In the 3 patients with measurable ADA titers at multiple time points, ADA titers decreased to undetectable levels during continued treatment. Since ADA development was transient and does not appear to affect efficacy, the potential risk of immune tolerance induction is also not justified in this patient population at this time.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application as there were no decisional issues that required input from the Advisory Committee during the review cycle.

⁹ Wang J, et al. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention and treatment. *Nat Biotechnol* 2008;26:901-8.

¹⁰ Banugaria SG, et al. The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease. *Genet Med* 2011;13:920-36.

¹¹ Banugaria SG, et al. Bortezomib in the rapid reduction of high sustained antibody titers in disorders treated with therapeutic protein: lessons learned from Pompe disease. *Genet Med* 2013;15:123-31.

10. Pediatrics

Sebelipase alfa was granted an orphan product designation on July 1, 2010. Therefore, the regulations that pertain to the Pediatric Equity in Research Act (PREA) do not apply to sebelipase alfa. The submission was not presented to the Pediatric Review Committee (PeRC).

The Division consulted the Division of Pediatric and Maternal Health (DPMH) to aid in the review of the labeling. The reader is referred to the DPMH consultation reviews by Dr. E. Hausman (Pediatrics), dated May 12, 2015, and Dr. L. Sahin (Maternal Health), dated June 9, 2015, for details. The DPMH recommendations have been incorporated into final labeling.

11. Other Relevant Regulatory Issues

Financial Disclosures

The Clinical reviewers indicated in their reviews that the Applicant adequately disclosed financial arrangements with the clinical investigators, and that these arrangements did not raise concern over the integrity of the data. The reader is referred to Clinical Investigator Financial Disclosure Forms included in Clinical reviews.

Office of Scientific Investigations

The reader is referred to the OSI review by Dr. S. Leibenhaut, dated June 22, 2015, for complete information.

The Clinical review team selected four clinical sites (Boston Children's Hospital, MA [PI: E. Neilan]; Central Manchester University Hospitals, UK [PI: S. Jones]; Centre de Reference Maladies, France [PI: V. Valayannopoulos]; and Hospital Infantil de México, Mexico [PI: A. Consuelos]) and three contract research organizations (b) (4)

(b) (4) for inspection, predominantly based on their high enrollment rate and their roles in central reading of important efficacy parameters, respectively. The Applicant was also inspected because sebelipase alfa is a new molecular entity (NME). Inspection of the (b) (4) found that the original procedure for blinding of timepoints for liver MRI in Protocol LAL-CL02 was not followed; however, the Applicant provided an erratum to the clinical study report to explain this issue. Although violations were cited during inspection of the Applicant, these violations were considered minor. The inspector concluded that all clinical sites and the contract research organizations appear reliable and the Applicant appears to have adequately fulfilled the sponsor responsibilities. The final classifications of all clinical sites and contract research organizations are no action indicated (NAI), and the final classification for the Applicant is voluntary action indicated (VAI).

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 LAL deficiency is a rare pediatric disease based on the criteria specified in Section 529 of the Federal Food, Drug, and Cosmetic Act. The Office of Orphan Products Development (OOPD) has accepted that the prevalence of LAL deficiency in the U.S. is less than 200,000, and that more than 50% of LAL deficiency patients are 18 years of age or younger. Therefore, the OOPD has determined that LAL deficiency 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 May 14, 2015, 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 “Kanuma” is acceptable. The reader is referred to the Proprietary Name review by M. Barlow, dated December 9, 2014, for details.

Specific Labeling Issues

Multiple labeling negotiations occurred between the Applicant and the review team during the review cycle. Key changes to the labeling are summarized below.

Section 2: Dosage and Administration

- Divided Subsection 2.1 (Dosage) into “Patients with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life” and “Pediatric and Adult Patients with LAL Deficiency” in order to provide clear dosing instructions for each patient population.
- For patients with rapidly progressive LAL deficiency presenting within the first 6 months of life, added a dosing instruction to increase to 3 mg/kg once weekly if an optimal clinical response is not achieved.
- Revised Subsection 2.2 (Preparation Instructions), with input from the Division of Medication Error Prevention and Analysis (DMEPA), to provide step-by-step instructions on how to calculate the total dose, number of vials, and volume of 0.9% Sodium Chloride for dilution.
- Added weight-based total infusion volumes for the 3 mg/kg dose to the table containing infusion volumes for the 1 mg/kg dose.
- Since available data suggest that product handling may contribute to inline filter occlusion, emphasized the instruction with an underline not to shake the vials or the prepared infusion.

Section 5: Warnings and Precautions

- For Subsection 5.1 (Hypersensitivity Reactions Including Anaphylaxis), included patient data from all ongoing and completed trials (N=106) to assess the incidence of hypersensitivity reactions, including anaphylaxis, in all patients exposed to sebelipase alfa.
- Added a separate subsection on “Hypersensitivity to Eggs or Egg Products.”

Section 6: Adverse Reactions

- For Subsection 6.1 (Clinical Trials Experience), described the safety data of 75 patients who completed two clinical trials submitted to support the marketing approval of Kanuma (66 patients from LAL-CL02 and 9 patients from LAL-CL03).
- Deleted (b) (4)
- Included more detailed information on transient hyperlipidemia observed upon initiation of sebelipase alfa treatment, including the number and percentage of patients experiencing the event and maximum mean percentage increase for LDL-c and triglycerides.
- Divided Subsection 6.2 (Immunogenicity) into “Patients with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life” and “Pediatric and Adult Patients with LAL Deficiency.”

Section 8: Use in Specific Populations

- Removed (b) (4).
- Revised Subsections 8.1 (Pregnancy) and 8.2 (Lactation) to be consistent with the format described in the “Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR) published on December 4, 2014. The reader is referred to the DPMH consultation review by Dr. Leyla Sahin, dated June 9, 2015, for details.

(b) (4)

Section 12: Clinical Pharmacology

- Removed (b) (4) from Subsection 12.1 (Mechanism of Action) and included information on clinical manifestation of LAL deficiency.
- Removed (b) (4)
- Presented the PK profiles of pediatric and adult patients with LAL deficiency by age group (4-11 years old, 12-17 years old, and ≥ 18 years old).

Section 13: Nonclinical Toxicology

- Added Subsection 13.2 (Animal Toxicology and/or Pharmacology) to include animal model data removed from Subsection 12.1.

Section 14: Clinical Studies

- Removed (b) (4) [REDACTED] included a general statement on greater reductions from baseline in ALT values and liver fat content (measured by MRI), compared to placebo. Added a statement that the significance of these findings as they relate to progression of liver disease in LAL deficiency has not been established.
- Included a statement that the effect of Kanuma on cardiovascular morbidity and mortality has not been established.
- Deleted (b) (4) [REDACTED]

In addition to the review team and the DPMH consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), and the Patient Labeling team from the Division of Medical Policy Programs (DMPP). Their comments and recommendations have been incorporated into final labeling. For final labeling agreements, the reader is referred to the approved product label for Kanuma (sebelipase alfa).

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend that Kanuma be approved for the following indication, pending resolution of the issues identified during facility inspection of the drug product fill and finish site:

Kanuma (sebelipase alfa) is indicated for the treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency.

Risk Benefit Assessment

Lysosomal acid lipase (LAL) deficiency is a serious and life-threatening disease. As there is currently no approved treatment for LAL deficiency, infants with rapidly fatal disease (Wolman disease) are managed with supportive care and pediatric and adult patients with LAL deficiency (CESD) are managed with dietary modification and lipid lowering medications to reduce LDL-cholesterol (LDL-c); however, none of these measures targets the underlying disease.

An open-label, historically controlled trial in infants with rapidly progressive disease (Wolman disease) demonstrated that 6 of 9 (67%) infants treated with Kanuma were alive at 12 months of age, whereas none of the 21 infants in the historical control group survived. The median age of the 6 surviving sebelipase alfa-treated patients was 18 months, which is well over 8 months by when all untreated patients in the natural history study had died. In addition, growth improved with continued treatment in surviving patients.

A double-blind, placebo-controlled trial in 66 pediatric and adult patients with LAL deficiency (CESD) demonstrated a statistically significant improvement from baseline in LDL-c levels and other parameters related to LAL deficiency in those treated with Kanuma compared with

placebo after 20 weeks of treatment. The extension trial data demonstrated continued improvements in these measures.

The safety profile was generally comparable to other enzyme replacement therapies, and no unexpected risks were identified during pre-marketing clinical trials. Hypersensitivity reactions, including anaphylaxis, are known serious adverse reactions associated with enzyme replacement therapy, and the risks and mitigation strategies are communicated through the labeling.

There are currently no products approved for patients with this serious and life-threatening disease. In light of this medical need and compelling clinical trial data, I believe the benefits outweigh the known risks associated with the use of this product. Therefore, I agree with the reviewers that Kanuma should be approved for treatment of LAL deficiency, once the issues identified during facility inspection of the drug product fill and finish site have been adequately addressed.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not recommended.

Recommendation for other Postmarketing Requirements and Commitments

The following PMCs are being negotiated at the time of completion of this review:

Clinical

1. Evaluate the long-term, prospective clinical outcomes of treatment with sebelipase alfa in adult and pediatric patients with LAL deficiency, including but not limited to progression of liver and cardiovascular diseases and changes in anthropometric assessments (i.e., length/height z-scores, and weight z-scores). At a minimum, liver assessments will include results of liver biopsies and imaging studies, changes in liver synthetic function, evidence for clinical progression to end stage liver disease (e.g., assessed by the Model for End-Stage Liver Disease [MELD] score), receipt of liver transplantation, and fatal outcomes. Cardiovascular assessments will include incidence rates of non-fatal stroke, myocardial infarction, and cardiovascular death. Additional evaluations will include dosing regimens administered and reasons for any dose modifications. This study will also collect data on the occurrence of any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Eligible patients will be enrolled over an initial 3-year period and followed for a minimum of 10 years from the time of enrollment or until death, whichever comes first. This study may be conducted as a separate study or as a sub-study within the Lysosomal Acid Lipase registry.

Drug Substance Quality Microbiology

2. Increase the bioburden test volume for (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.

3. Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.
4. Improve the endotoxin method for the (b) (4) samples by optimizing the endotoxin test procedures.
5. Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the (b) (4) and drug substance endotoxin test using the modified endotoxin method involving the use of (b) (4) sample preparation system. Provide the validation information and data.

Drug Product Quality Microbiology

6. [REDACTED] (b) (4)
7. Validate the [REDACTED] (b) (4)
[REDACTED]
If the [REDACTED] (b) (4) is revised based on the validation study, update the BLA file accordingly.
8. The microbial retention study [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
9. Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes [REDACTED] (b) (4). Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.
10. [REDACTED] (b) (4)
11. Conduct studies to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

Drug Substance Quality

12. Characterize the potential levels of [REDACTED] (b) (4) [REDACTED] in the drug substance.
13. Develop and implement a drug substance release test to quantify the percent compositions of the N-terminal variants.
14. To improve control of the N-linked glycan profile, identify for the current HPAEC-PAD method peaks representative of [REDACTED] (b) (4) [REDACTED] and establish drug substance

- release specifications for the critical peaks or groups of peaks. Alternatively, develop an alternative method with better resolution to control the glycan profile, such as (but not limited to) the (b) (4) characterization tests.
15. Conduct studies to improve the formulation to reduce or eliminate the potential for formation of visible proteinaceous particles and other insoluble protein aggregates. If a significantly improved formulation is identified, develop the improved formulation for the commercial product.

Drug Product Quality

16. Develop and implement an improved SDS-PAGE or another purity test to quantitate high molecular weight product-related species with greater sensitivity and precision than the current SDS-PAGE method.
17. Implement the (b) (4) test method for drug product release specifications.
18. Implement an assay for uptake of sebelipase alfa into (b) (4) for drug product release specifications.
19. Develop and implement a (b) (4) receptor binding assay for drug product release specifications.
20. Conduct studies to determine whether the (b) (4) receptor binding assays are stability-indicating. Implement the stability-indicating assays into the drug product stability specifications with acceptance criteria supported by stability data.
21. Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent values for specific activity.
22. Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses.
23. Conduct worst-case simulated or worst-case real world shipping studies for both the drug substance and the drug product to assess the potential impact of shipping conditions on product quality.
24. Characterize the potential of rhLAL to form oxidized variants and deamidated variants and determine whether variants identified are stability-indicating. Implement changes to the drug substance and drug product control strategies as warranted by the data.

Recommended Comments to Applicant

No additional comments to the Applicant are recommended at this time.

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

/s/

JESSICA J LEE
09/06/2015