

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**125561Orig1s000**

**SUMMARY REVIEW**

Addendum to DGIEP review of BLA 125561, Alexion Pharmaceuticals Inc. (formerly Synageva BioPharma Corp.) KANUMA / sebelipase alfa

Alexion's responses to FDA's observations and requests regarding manufacturing operations at (b) (4) and details of its plans to transfer manufacturing to an alternative site ( (b) (4) ), submitted on September 2, 2015, were considered a major amendment triggering a 3 month review clock extension.

On October 14, 2015, Alexion submitted its plans to evaluate the comparability of Kanuma drug product manufactured at the (b) (4) site to Kanuma drug product manufactured at the (b) (4) site, and a schedule for submissions of the data supporting this comparability assessment. On November 25, 2015, Alexion amended the BLA to add (b) (4) as a drug product manufacturing and sterility testing site and to remove the (b) (4) site from any manufacturing and testing activities. Review of the submitted data support comparability of the (b) (4) drug product to (b) (4) drug product. The BLA, as amended, is therefore approvable.

I provide the recommendation of the Division of Gastroenterology and Inborn Errors Products to approve Kanuma (sebelipase alfa) for the treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency to the Signatory, Dr Julie Beitz.

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/s/  
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ANDREW E MULBERG  
12/07/2015

## Summary Review for Regulatory Action

|                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Date</b>                                       | September 8, 2015                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>From</b>                                       | Andrew E. Mulberg, MD, FAAP, CPI                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Subject</b>                                    | Division Deputy Director Summary Review                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>NDA/BLA #</b>                                  | BLA 125561<br>N/A                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Applicant Name</b>                             | Alexion Pharmaceuticals Inc. (formerly Synageva BioPharma Corp.)                                                                                                                                                                                                                                                                                                                                                                |
| <b>Date of Submission</b>                         | January 8, 2015 (rolling submission began October 21, 2014)                                                                                                                                                                                                                                                                                                                                                                     |
| <b>PDUFA Goal Date</b>                            | September 8, 2015                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Proprietary Name / Established (USAN) Name</b> | KANUMA / sebelipase alfa                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Dosage Forms / Strength</b>                    | 20 mg/10 mL (2 mg/mL) injection, for intravenous use<br><u>Dosage:</u> <ul style="list-style-type: none"> <li><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></li> <li><i>Pediatric and adult patients with LAL deficiency - 1 mg/kg IV every other week</i></li> </ul> |
| <b>Proposed Indication(s)</b>                     | Treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency                                                                                                                                                                                                                                                                                                                                                |
| <b>Action/Recommended Action for NME:</b>         | <i>Approval pending Clearance of All Inspection-Related Compliance Issues</i>                                                                                                                                                                                                                                                                                                                                                   |

|                                                                                                                                       |                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>Material Reviewed/Consulted</b>                                                                                                    | <b>Names of discipline reviewers</b>                                                                         |
| OND Action Package, including:                                                                                                        |                                                                                                              |
| Medical Officer Review                                                                                                                | Juli Tomaino/Lauren Weintraub                                                                                |
| CDTL Review                                                                                                                           | Jessica Lee, MD                                                                                              |
| Product Quality (DBRR II/OBP) <ul style="list-style-type: none"> <li>Drug Substance</li> <li>Drug Product</li> </ul> Secondary review | C. Downey, Ph.D. (Lead) and S. Williams, Ph.D. (Assay Validation)<br>A. Arudchandran, Ph.D.<br>J. Liu, Ph.D. |
| Immunogenicity (DBRR III/OBP)                                                                                                         | J. Pedras-Vasconcelos                                                                                        |
| Product Quality Microbiology (DMA/OPF/OPQ) <ul style="list-style-type: none"> <li>Drug Substance</li> <li>Drug Product</li> </ul>     | B. Chi, Ph.D.<br>C. Thomas, Ph.D.                                                                            |

**Deputy Division Director Review**  
**Kanuma (sebelipase alfa)**  
**September 8, 2015**

|                                                                                                                                 |                                           |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Nonclinical (DGIEP)<br><ul style="list-style-type: none"> <li>Primary review</li> </ul> Tertiary review                         | T. Chakraborti, Ph.D.<br>A. Jacobs, Ph.D. |
| Clinical Pharmacology (DCP-3 OCP)                                                                                               | J. Fang, Ph.D. and Sarah Dorff, Ph.D.     |
| Statistics (DB III)                                                                                                             | B. Vali, M.S.                             |
| Clinical site inspections (DCCE/OSI)                                                                                            | S. Leibenhaut, M.D.                       |
| Manufacturing site inspections (DMPQ/OC)                                                                                        |                                           |
| Consultation review (DAVP)<br><ul style="list-style-type: none"> <li>Liver endpoints</li> <li>Virology</li> </ul>               | P. Mishra, M.D.<br>L. Mishra, Ph.D.       |
| Consultation review (DMEP)                                                                                                      | J. Golden, M.D.                           |
| Consultation review (DMGP/OIVD/CDRH)<br>Evaluation of pathology images and reports                                              | P. Jha, M.D.                              |
| Consultation review (DPMH)<br><ul style="list-style-type: none"> <li>Pediatrics</li> <li>Maternal Health</li> </ul>             | E. Hausman, M.D.<br>L. Sahin, M.D.        |
| Consultation review (OOPD)                                                                                                      | J. Milto, M.D.                            |
| Proprietary name review (DMEPA)                                                                                                 | M. Barlow, R.N.                           |
| Labeling review (DMEPA)                                                                                                         | M. Barlow, R.N.                           |
| Labeling review (OBP)                                                                                                           | J. Abdus-Samad, Pharm.D.                  |
| Labeling review (OPDP)                                                                                                          | A. Adeleye, Pharm.D.                      |
| Clinical (DGIEP)<br><ul style="list-style-type: none"> <li>Wolman disease</li> <li>Cholesteryl ester storage disease</li> </ul> | L. Weintraub, M.D.<br>J. Tomaino, M.D.    |

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; DMPQ, Division of Manufacturing and Product Quality; OC, Office of Compliance; DAVP, Division of Antiviral Products; DMEP, Division of Metabolism and Endocrinology Products; DMGP, Division of Molecular Genetics and Pathology; OIVD, Office of In Vitro Diagnostic Device Evaluation and Safety; 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.

## Signatory Authority Review Template

### 1. Introduction

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

- 1) Kanuma is approved (b) (4) for the treatment of pediatric and adult patients with lysosomal acid lipase (LAL) deficiency (i.e., cholesteryl ester storage deficiency [CESD]).

In this BLA, the applicant submits the following two pivotal trials for registration of Sebelipase alfa, herein referred to as Kanuma. The BLA consisted of a two pivotal 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. 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 from a retrospective natural history study conducted in Wolman disease (LAL-1-NH01) was used as a comparator group. To support the indication of Kanuma for the childhood-onset LAL deficiency, aata submitted from Study LAL-CL02 was performed as a double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of sebelipase alfa in patients  $\geq 4$  years of age with cholesteryl ester storage deficiency (CESD). Study LAL-CL02 compared sebelipase alfa 1 mg/kg administered every other week as an IV infusion as compared to placebo. Based on the data collected during Study LAL-CL02, low density lipoprotein cholesterol (LDL-c) appears to be the most suitable endpoint to assess efficacy in patients with CESD. LDL-c is part of 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. While this trial was not designed to assess the relationship between improvement in LDL-c and long-term risk of cardiovascular disease, a reduction in LDL-c likely represents a clinical benefit in this patient population since patients with CESD exhibit dyslipidemia and are at risk for atherosclerosis. In fact, over half of the patients enrolled in Study LAL-CL02 had a baseline LDL-c  $\geq 190$  mg/dL, placing them at high risk for coronary heart disease. Additionally, unlike lipid lowering medications, which do not address the underlying cause of LAL deficiency, sebelipase alfa is an enzyme replacement therapy specifically targeted to correct the underlying defect that results in the disease manifestations seen in CESD. Hence, this assessment of efficacy will focus on the change from baseline in LDL-c in patients with CESD treated with sebelipase alfa.

## 2. Background

Lysosomal lipase activity (LAL) has been identified to be relevant in the cellular processes of cholesterol metabolism and lipoprotein homeostasis. The enzyme when there is deficient activity of LAL results in massive cholesterol and TG deposition in many tissues. Two major allelic disorders range from the most severe infantile-onset Wolman disease (WD) and the milder late-onset cholesteryl ester storage disease (CESD resulting from deficient lysosomal acid lipase/acid cholesteryl ester hydrolase. The residual amount of enzyme activity differs in both disorders and the clinical and biochemical consequences are extremely dissimilar. CESD patients present with hepatic manifestations, survive beyond middle age, and develop atherosclerosis. WD is lethal within the 1st year of life. Newborns die from excessive **storage** of lipids in most tissues before atherosclerosis can develop. Adrenal calcification is specific to WD and is not common in CESD. Cholesteryl esters as well as triglycerides are markedly elevated in tissues of WD patients, while only mild elevations of triglycerides accompany the pathologic cholesteryl ester elevations in CESD.<sup>1</sup>

The biochemical metabolism is illustrated below demonstrating the criticality of the LAL activity in lipoprotein metabolism focusing on the differences in Wolman and CESD. Deficiency of LAL activity leads to accumulation of cholesteryl esters and triglycerides and depending on disease activity has different phenotypic expression as reflected below.

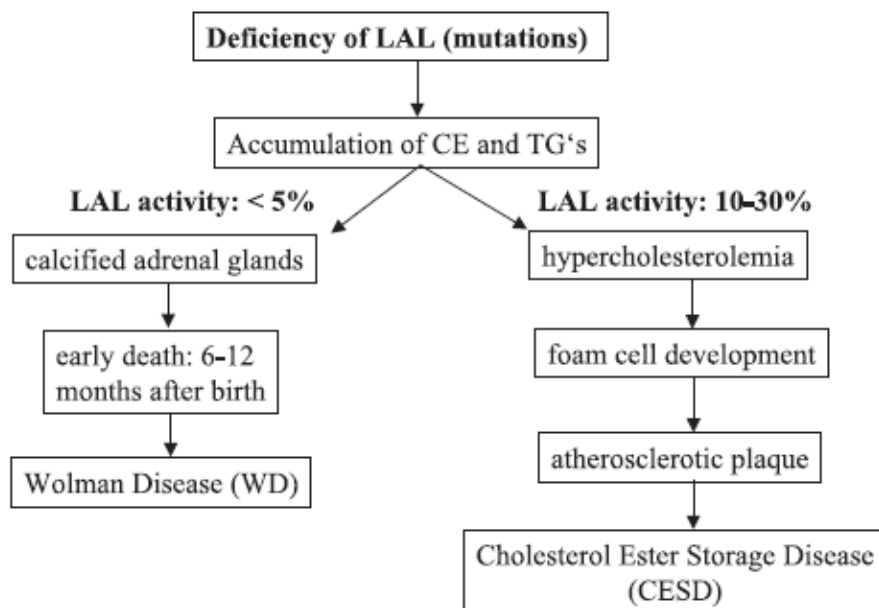


**Figure 1:** Differences of the two diseases, Wolman disease and cholesteryl ester storage disease, caused by deficiencies of LAL. For both diseases, there is an accumulation of cholesteryl esters and triglycerides in the cells, by which cholesteryl ester storage disease

<sup>1</sup> Aslanidis C, Ries S, Fehringer P et al. Genetic and Biochemical Evidence That CESD and Wolman Disease Are Distinguished by Residual Lysosomal Acid Lipase Activity. *Genomic* **33**, 85–93 (1996)

is the benign form, which can be treated with statins and a low-fat diet. The reason is the more active LAL in these patients. Wolman patients, dying within the first 12 months of their lives, show only residual LAL activity.

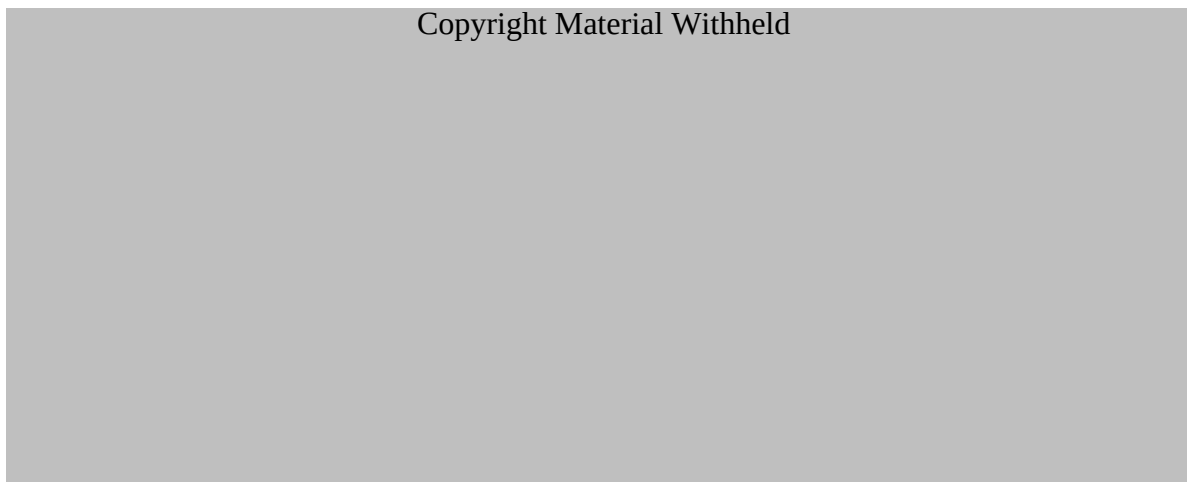
Clinical differences in presentation and manifestations of disease are illustrated below in Table 1:

|                                 | <b>Infantile-Onset (Wolman)</b>                                                                                                                                                      | <b>Late-Onset (CESD)</b>                                                                                                                                               |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Residual enzyme activity</b> | None or minimal                                                                                                                                                                      | Some                                                                                                                                                                   |
| <b>Age of onset</b>             | Infancy                                                                                                                                                                              | Childhood through adulthood                                                                                                                                            |
| <b>Life expectancy</b>          | Death within 1 <sup>st</sup> year of life                                                                                                                                            | Beyond middle age                                                                                                                                                      |
| <b>Substrate accumulation</b>   | Triglycerides & cholesteryl esters                                                                                                                                                   | Primarily cholesteryl esters                                                                                                                                           |
| <b>Disease manifestations</b>   | <ul style="list-style-type: none"> <li>• Growth failure</li> <li>• Malabsorption</li> <li>• Hepatosplenomegaly</li> <li>• Liver disease</li> <li>• Adrenal calcifications</li> </ul> | <ul style="list-style-type: none"> <li>• Liver disease: variable progression to cirrhosis</li> <li>• Premature cardiovascular disease, hypercholesterolemia</li> </ul> |
| <b>Cause of death</b>           | <ul style="list-style-type: none"> <li>• Malnutrition/growth failure</li> <li>• Severe liver failure</li> <li>• Multisystem failure</li> </ul>                                       | <ul style="list-style-type: none"> <li>• Complications of atherosclerosis</li> <li>• Cirrhotic liver failure</li> </ul>                                                |

**Table 1: Phenotype and presentation of LAL Deficiency: reproduced from Acting Commissioner Internal Briefing Held, August 26, 2015**

The cellular mechanism of LAL activity leading to atherosclerosis is illustrated below clearly in Figure 2: The mechanistic pathway leads to atherosclerotic plaques.

### Figure 2: Mechanism of LAL Activity and Cholesterol Trafficking



Reproduced from reference 2 cited below.

Lipid metabolism in presence of active LAL (A) and in a LAL-deficient cell (B). LDL and other lipoproteins enter the cell via endocytosis and are hydrolyzed in the lysosomes by LAL releasing cholesterol, free fatty acids and glycerol. LAL-deficiency or reduced activity leads to an accumulation of cholesteryl esters and triglycerides in the lysosomal compartment, which may promote formation of atherosclerotic plaques. The ABCA1 transporter converts pools of late endocytic lipids associated with endocytosed apo A-I which is released from the cell as nascent HDL (105). Please note that cholesterol is liberated from LDL cholesteryl ester in the hydrolytic compartment containing LAL and then moves to late endosome/lysosome before reaching the ER (75). Abbreviations used are: LDL: low-density lipoprotein; HDL: high-density lipoprotein; ER: endoplasmic reticulum; ACAT: Acyl-coenzyme A-cholesteryl-acyl-transferase; NCEH: neutral cholesteryl ester hydrolase.<sup>2</sup>

### 3. CMC

Elosulfase alfa is supplied as a concentrated solution for infusion (1 mg/mL) requiring of Therapeutic Proteins reviewers have recommended approval of BLA 125460, and I agree with their assessments. The reader is referred to the reviews for further details.

#### CVM issues

Alexion Pharmaceuticals, Inc. has developed a line of chickens that are genetically engineered to produce rhLAL in their egg whites. The sponsor has two FDA-regulated articles: (1) a recombinant (rDNA) construct in a lineage of GE chickens that CVM regulates under the new animal drug authorities<sup>3</sup> and (2) a therapeutic biologic product

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<sup>2</sup> Zschenker O, Illies T and Ameisy D. Overexpression of Lysosomal Acid Lipase and Other Proteins in Atherosclerosis. J. Biochem. 140, 23–38 (2006).

<sup>3</sup> The rDNA construct meets the Federal Food, Drug, and Cosmetic Act (FD&C Act) drug definition because it is an article intended to affect the structure or function of the body of the animal. It is regulated under the new animal drug provisions of the FD&C Act and as a major Agency action; an approval also triggers the environmental review requirements of the National Environmental Policy Act.

(sebelipase alfa, the rhLAL protein purified from GE hen egg whites) that CDER regulates under the human new drug authorities. Alexion's GE chicken line produces rhLAL in its egg whites. The GE egg whites are considered the source of the unprocessed bulk drug substance that is purified to produce the human drug product Kanuma used as an enzyme replacement therapy in the treatment of humans with LAL deficiency disease. CVM is regulating production of the GE chicken and its gene expression product, which produces the starting material (the egg white containing the rhLAL) for manufacture of the human drug product Kanuma. CVM and CDER regulations overlap with respect to production of the gene expression product in the egg, egg collection and initial processing, and up to the egg crack. CDER's regulation of the human drug product covers production steps from the egg crack through all subsequent egg-white-related and purification activities. CDER regulations also encompass review of the safety and effectiveness of the human drug product Kanuma.

CVM's review found that:

- the rDNA construct encodes human LAL sequence and, as integrated in the genome of Synageva BioPharma Corp. Lysosomal Acid Lipase (line) C (SBC LAL-C) animals, is capable of expressing recombinant hLAL;
- the rDNA construct is safe to the target animal;
- other than for the GE trait intentionally introduced, SBC LAL-C GE chickens are phenotypically similar to non-GE chickens;
- the rDNA construct is stably integrated and inherited in a Mendelian fashion across multiple generations;
- the sponsor has prepared an environmental assessment (EA) and CVM is prepared to issue a finding of no significant impact on the environment once the EA is finalized because the animals and their potentially edible products will be sufficiently physically contained and disposed of by incineration and there is no risk to the human environment of the United States;
- ORA has completed biomonitoring inspections of the sponsor's animal facilities and found them to be acceptable; CVM scientists present at the inspections found the animal husbandry, containment, personnel, and record keeping sufficient to ensure safety and security of the GE animal and animal products (eggs, waste, etc.);
- the sponsor has provided assurances that SBC LAL-C chickens will not enter the food supply; in the event of an inadvertent release, CVM has determined that it would have a low level<sup>4</sup> 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;
- the sponsor has validated the claim that SBC LAL-C GE hen egg whites contain rhLAL (i.e., it has established effectiveness); and a rigorous post-market record-keeping and reporting program has been developed.

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<sup>4</sup> For biopharm animals (i.e., 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.

### **CMC/Product Quality Review**

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

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

### **CMC/Immunogenicity Review**

The reader is referred to the Immunogenicity review by Dr. J. 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.

As noted by Dr. Lee in her CDTL memorandum, 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. Seven of the 9 infants had at least one post-treatment anti-drug antibody (ADA) assessment. Of the 7 patients with immunogenicity data, 4 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 had 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. 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.

#### 4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Pharmacology/Toxicology review by Dr. T. Chakraborti, dated June 8, 2015, for complete information. Relevant details to this product development include the use of nonclinical disease models which have accelerated the product development from early stages. 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. This Signatory would encourage the application of any further developmental approaches to allometric scaling to understand more fully the dosing regimen in infants. These issues are discussed below. The Nonclinical review team has recommended approval, and I agree with their recommendation. The reviewers have not recommended PMCs or PMRs.

#### 5. Clinical Pharmacology

The reader is referred to the primary review for this discipline for complete details. I wish to comment on the CDTL memorandum that commented that there is no ER relationship in the infant population with LAL deficiency. Specifically she cites that “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.”

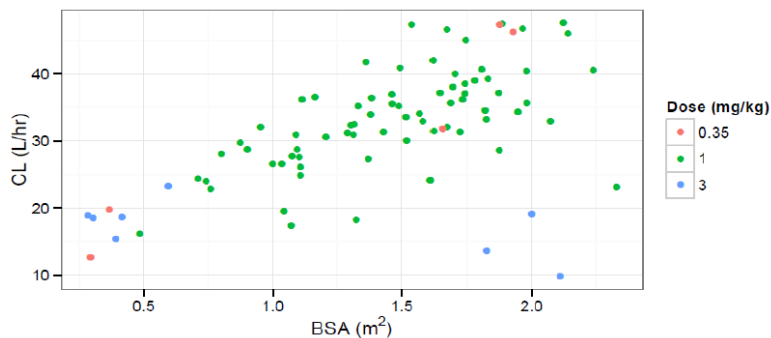
**A. Infantile-onset LAL deficiency: Study LAL-CL03**

It is clear that the exposure response relationship could not be established in infants but more to the likely possibility of the paucity of data available to support such an exposure response relationship. There is an unclear pathophysiological explanation for the obvious ER relationship illustrated for LDL processing which is as noted is an intracellular processing issue. The difference of LDL processing in CESD from Wolman’s and the target for Kanuma in the infant population remains unclear to me. Therefore, obtaining additional PK data from the infant Wolman population would be ideal to maximize the dose selection for greatest efficacy.

From a dosing perspective, I have concerns that additionally the criteria for dose escalation in the infants was not determined prospectively since the criteria for clinical deterioration and clinical response were not protocol driven according to Dr. Lee. She notes: “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).”

This Signatory also agrees that the dose requires optimization as quickly as possible but is unsure that the dose identified as 1 mg/kg with escalation to 3 mg/kg will be optimal for all infants. Support for this hypothesis comes from additional analysis of the PK characterization of sebelipase. Dr. Lee notes 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 3, the sebelipase alfa clearance increased with increasing body surface area, supporting a weight-based dosing regimen. It is interesting to note that the BSA below 0.5 had a wide distribution of clearance with dose. It appears that the higher 3 mg/kg dose had a more stable clearance but does support that a higher dose may be more effective and should be initiated as early as evidence of lack of improvement in the infant with Wolman’s.

**Figure 3: Characterization of PK Parameters in CESD:**



Reproduced from CDTL memorandum, Dr. Jessica Lee

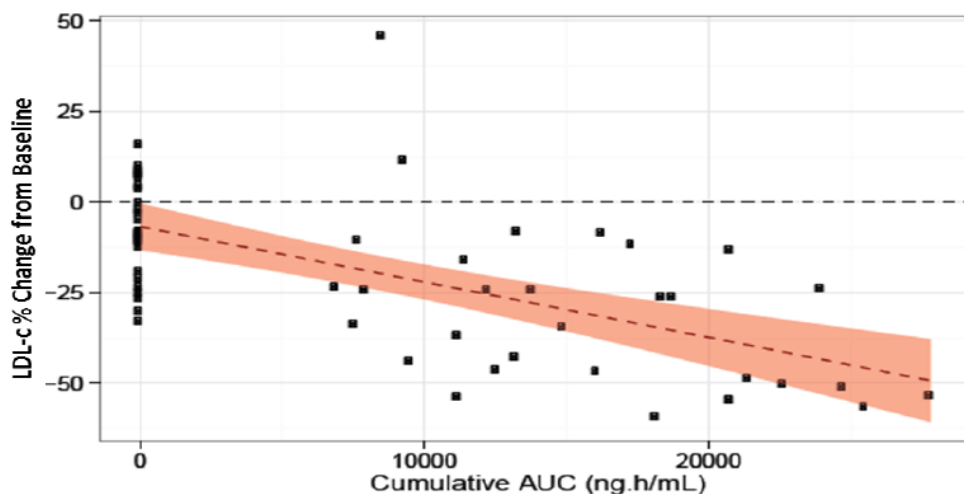
I agree that the dose regimen is appropriate for the approval of the indication but believe additional dosing studies should be performed to identify the true range of effective and required dosing for maximizing survival and the effect in reduction of infant mortality. It is agreeable that the endpoint of survival was proven but the absence of sufficient data to support an ER relationship in infants with Wolman's remains an important issue for future clarification. Further discussion on implications of the optimal dose regimen will be discussed below.

#### **B. 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. As illustrated through the ER relationship observed in study, Dr Lee notes from the older children and adult study of LAL deficiency, there indeed is an ER relationship. "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 5 below, 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 4 below reflects the documentation of an ER relationship as discussed above in the CESD population and supports that there is potentially more to understand on the serum exposure of this lysosomal targeted product. It raises important questions regarding dose selection and whether modeling and simulation should be more aggressively pursued prior to initial vulnerable population exposures.

#### **Figure 4: Exposure Response relationship of LAL Activity to LDL Concentration Reflected as %Change from Baseline**



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

## 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 Applicant has submitted a pivotal trial in infants consisting of 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. 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 from a retrospective natural history study conducted in Wolman disease (LAL-1-NH01) was used as a comparator group. The reader is referred to the Clinical reviews of Drs. Tomaino and Weintraub for further details. The Clinical reviewers and CDTL and Statistical Reviewer all recommended approval for both age cohorts for the indication. I will focus on salient elements that deserve further discussion for each age cohort.

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

#### Analysis of Primary Endpoint

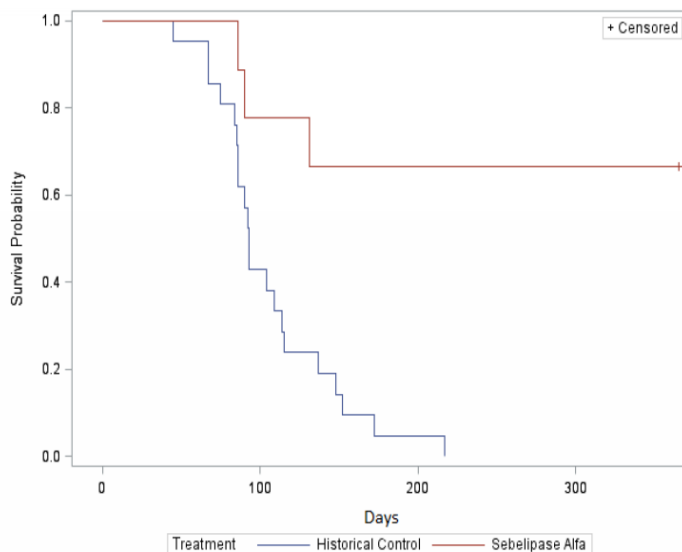
The primary endpoint was time to death from birth up to Month 12. Efficacy of sebelipase alfa was assessed by comparing the survival of 9 sebelipase alfa-treated patients at 12 months of age with an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. 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 1: 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<br>(N = 9) | Historical Control<br>(N = 21) | Treatment Difference<br>(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                                                         |

**Figure 5: Kaplan-Meier survival analysis from birth up to Month 12 (sebelipase alfa-treated patients in LAL-CL03 vs. historical control patients in LAL-1-NH01)**



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. In toto in the rapidly progressive cohort, it is clear that there is a survival advantage and improvement of growth in surviving infants.

Growth clearly improved as noted by Dr. Weintraub and illustrated in the accompanying growth curves of individual subjects but not definitively apparent of the association of a need for higher dose regimen of 3 mg/kg in all patients (see Figure 6 below):

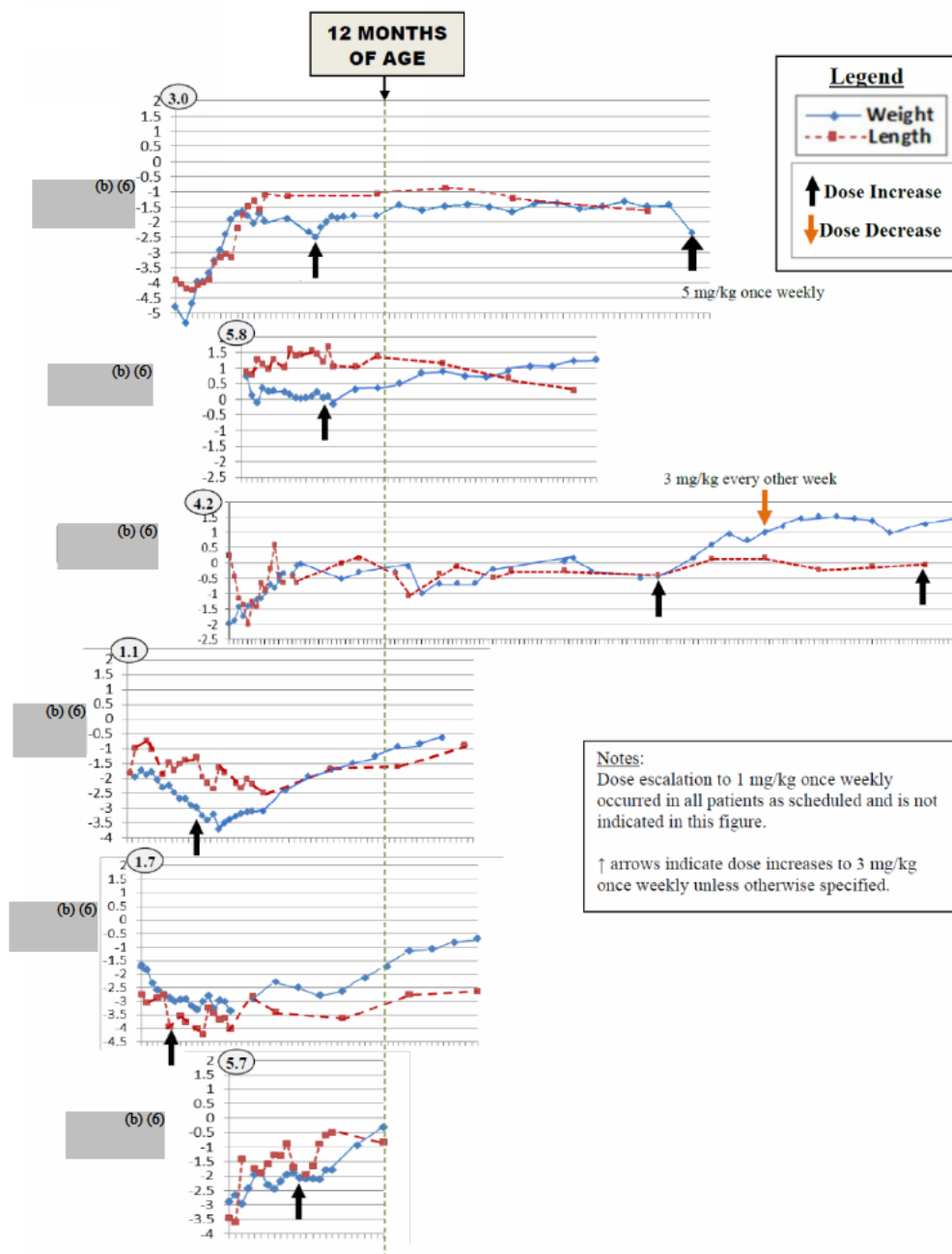


**Figure 6: Growth Curves and Response to Dose Escalation in Individual Subjects with Rapidly Progressive LAL Deficiency**

Dose escalation was determined with poor attention to pre-specified protocol determined criteria for suboptimal treatment response or no pre-specified definitions for organomegaly described in either the clinical study protocol or the clinical study report. These included Early (within the first 3 months of treatment): at least 2 of the following criteria:

- Failure to gain an average of 5 g /kg body weight per day, and the presence of either of the following:
  - WHO weight-for-length (WFL) or weight-for-height (WFH) z-score < -2
  - WHO length-for-age (LFA) or height-for-age (HFA) z-score < -2
- Albumin < 3.5 g/dL
- Alanine aminotransferase (ALT) > 2x upper limit of normal (ULN)
- Ongoing requirement for blood and/or platelet transfusion.

Late (after at least 3 months of treatment): any clinical important manifestation of LAL Deficiency (on clinical examination, laboratory assessment, or imaging) that had not improved from baseline, had improved and plateaued (based on at least 3 assessments) but had not yet normalized, or failed to normalize within 12 months of treatment. Examples of a suboptimal response could include but are not restricted to: a decrease in WFA crossing more than 2 major centiles, serum transaminase levels meeting the above criteria, albumin < 3.5 g/dL, or the presence of hepatomegaly, splenomegaly, or lymphadenopathy. For the 3 patients with “early” dose escalation, the listed reasons technically don’t meet the pre-specified criteria but all patients responded clinically. The reasons for dose escalation are reproduced below in Table 3:

**Table 3: Dose escalation to 3 mg/kg qw due to Suboptimal Clinical**

| Subject ID | No. of infusions at ≤0.35 mg/kg qw | No. of infusions at 1 mg/kg qw | First Infusion at 3 mg/kg qw | Suboptimal Response Criteria Used <sup>a</sup> | Criterion Not Met <sup>a</sup>                                                          |
|------------|------------------------------------|--------------------------------|------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------|
| (b) (6)    | 2                                  | 21                             | Week 23                      | Late                                           | WFA plateaued; also hepatomegaly                                                        |
|            | 2                                  | 10                             | Week 14                      | Late                                           | WFA plateaued                                                                           |
|            | 4 <sup>b</sup>                     | 86                             | Week 91                      | Late                                           | Mesenteric lymphadenopathy                                                              |
|            | 2                                  | 10                             | Week 12                      | Early                                          | Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2 |
|            | 2                                  | 4                              | Week 6                       | Early                                          | Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2 |
|            | 2                                  | 8                              | Week 10                      | Early                                          | Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2 |

Source: Listing 16.2.5.1, Safety Committee Meeting Minutes (Appendix 16.1.9), and Sponsor data on file

HFA = height-for-age; LFA = length-for-age; qw= weekly; WFA = weight-for-age; WHO = World Health Organization

a - Early and late suboptimal response criteria are defined in Section 8.4.5.1

b - Subject initiated treatment under Temporary Use Authorisation and received doses of 0.2 mg/kg, 0.3 mg/kg, 0.5 mg/kg and 0.75 mg/kg at Weeks 0, 1, 2, and 3.

## B. 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.

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., patients with CESD). Much deliberation of the weakness of this proposed primary endpoint was made with the Sponsor as the endpoint does not necessarily serve as a reasonably likely surrogate for efficacy and cannot serve as a primary endpoint. Through discussion and an understanding of the pathophysiology of lipoprotein metabolism in this disorder as discussed above (see Figure 2), 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. 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. 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.

Dr. Lee in her CDTL memorandum notes that "At the completion of the 20-week double-blind period of the trial, LDL-c of less than 130 mg/dL (range that reduces the risk of developing coronary heart disease)<sup>5</sup> 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 baseline LDL-c of 130 mg/dL or greater." The clinical implications of this LDL reduction will be further addressed in the proposed PMC for the Sponsor discussed below in Section 13 below as noted by Dr. Lee who states: "Despite improvements in lipid parameters, the effect of sebelipase alfa on cardiovascular morbidity and mortality has not been established. In order to further evaluate the long-term clinical benefit of sebelipase alfa on cardiovascular diseases as well as liver outcomes, the Clinical reviewers have recommended the following postmarketing commitment study."

Drs. Tomaino and Lee both recommended Approval for the older child and adult cohort with CESD and this Signatory agrees with this assessment.

## 8. Safety

I concur with Dr. Weintraub's and Tomaino's medical review of the safety information which is summarized by Dr. Lee in the CDTL summary. There are no notable safety related issues associated with Kanuma administration as a biological therapeutic agent. The reader is referred to the individual safety review for further information. Briefly, the reader is referred to the Clinical review by Drs. Weintraub and Tomaino, complete

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<sup>5</sup> 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.

information. As noted by Dr Tomaino, the frequency of hypersensitivity reactions was low during the double-blind treatment period, and the majority of the signs and symptoms associated with the most severe reaction occurred in the one patient in the SA group described above. During the 20-week double-blind treatment period, no patients met the clinical criteria for anaphylaxis. Two out of 36 (6%) patients in the SA group experienced 10 hypersensitivity reactions likely related to SA, and 4/30 (13%) patients in the placebo group experienced 5 signs or symptoms that could be considered as a hypersensitivity reaction. While these reactions were temporally related to the infusion, the patients were receiving placebo infusions; therefore, it is unlikely that the signs and symptoms were related to a hypersensitivity reaction since these patients were receiving placebo. The adverse reactions reported from Study LAL-CL02 were similar to the adverse reactions known to be associated with enzyme replacement therapies. I do agree with the recommendation of the CDTL, Dr. Lee who discusses the issues of immune tolerance regimens as not being appropriate for this population.

Of note is Table 4, Listing of Deaths in Study LAL-CL03 reports on the deaths associated with this study. What is notable is the dosing regimen at the time of death which supports the current dosing regimen is critical for survival of these Wolamn infants. It is highly likely that the cause of death for these infants was associated with suboptimal response to Kanuma. According to the medical reviewer, Dr. Weintraub, she notes that subeect (b) (6) died 5 days after the first infusion with the mini-dose of 0.35 mg/kg which is no longer used. This patient died of multi-system organ failure. (b) (6) was receiving continuous blood products and inotropic support. (b) (6) developed worsening oliguria and abdominal distension, then developed bradycardia, acidosis, hypotension. Other case reports are noted below:

- (b) (6) died 6 days after the first infusion (also the mini-dose). “Despite frequent transfusions of red blood cells and administration of dipyridamole, the subject had marked decreases in hemoglobin level and platelet count. On day 5 after the infusion, the subject experienced a worsening of ascites that interfered with normal ventilation, and underwent abdominal paracentesis, which caused intraperitoneal bleeding. (b) (6) developed bradycardia, metabolic acidosis, hypotension, and died of cardio-respiratory failure secondary to peritoneal hemorrhage.”
- (b) (6) died after receiving 4 infusions (2 infusions at 0.35 mg/kg and 2 infusions at 1 mg/kg). “Death was 6 days after the last infusion. At study entry, the subject was being treated by the investigator for symptoms consistent with a Hemophagocytic lymphohistiocytosis (HLH)-like syndrome, including persistent anaemia, thrombocytopenia, and coagulopathy. The subject was receiving regular transfusions of red blood cells, plasma, and platelets. The cause of death was cardiac arrest thought to be secondary to a severe brain hemorrhage and possibly a worsening of HLH secondary to an abrupt cessation of dexamethasone” without authorization”.

|                                                     |
|-----------------------------------------------------|
| <b>Table 4: Listing of Deaths in Study LAL-CL03</b> |
|-----------------------------------------------------|

**Table 18: Listing of Deaths in Study LAL-CL03**

| Subject | Date of First IMP Infusion | Number of IMP Infusions Prior to Death | Dosing Regimen at Time of Death | Date of Death | Age at Death (months) | Cause of Death, as Reported by the Investigator |
|---------|----------------------------|----------------------------------------|---------------------------------|---------------|-----------------------|-------------------------------------------------|
| (b) (6) | (b) (6)                    | 1                                      | 0.35 mg/kg                      | (b) (6)       | 2.79                  | Liver failure secondary to Wolman disease       |
|         | (b) (6)                    | 1                                      | 0.35 mg/kg                      | (b) (6)       | 2.92                  | Massive intraperitoneal bleeding                |
|         | (b) (6)                    | 4 <sup>a</sup>                         | 1 mg/kg                         | (b) (6)       | 4.27                  | Cardiac arrest                                  |

Source: Table 14.3.2.5 and Listing 16.2.5.1

IMP = investigational medicinal product (sebelipase alfa)

<sup>a</sup> Two infusions at 0.35 mg/kg and 2 infusions at 1 mg/kg

The pathophysiological relationship of the reported HLH remains unclear.

## 9. Advisory Committee Meeting

No Advisory Committee meeting was held for this application.

## 10. Pediatrics

Sebelipase alfa was granted an orphan product designation on. Therefore, the regulations that pertain to the Pediatric Research Equity Act (PREA) do not apply to elosulfase alfa. The submission was not presented to the Pediatric Review Committee (PeRC). The Division consulted the Pediatrics and Maternal Health Staff (PMHS) to aid in the review of the labeling. The reader is referred to the PMHS consultation review by Dr. E. Radden, dated October 21, 2013, for details. The PMHS recommendations have been incorporated into final labeling.

## 11. Other Relevant Regulatory Issues

### Office of Scientific Investigations

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

### Rare Pediatric Disease Priority Review Voucher Program

The Rare Pediatric Disease Priority Review Voucher (RPDPRV) Program, established under the Food and Drug Administration Safety and Innovations Act (FDASIA), entitles the sponsor of a qualifying rare pediatric disease product application to receive a voucher for 'priority review' of any subsequent human drug application upon marketing approval of the product. The Applicant has submitted data to support that MPS IVA is a rare pediatric disease based on the criteria specified in Section 529 of the Federal Food, Drug, and Cosmetic Act. The Office of Orphan Products Development (OOPD) has accepted that the prevalence of MPS IVA in the U.S. is less than 200,000, and that no more than

32% of MPS IVA patients would survive beyond 18 years of age. Since the majority of MPS IVA patients would be younger than 18 years of age, the OOPD has determined that MPS IVA meets the FDASIA definition of a rare pediatric disease to be eligible for a voucher. The reader is referred to the OOPD consultation review by Dr. J. Milto, dated January 15, 2014, for complete information. A priority review voucher will be issued at the time of marketing approval.

#### **Inspection and Compliance Related Issues Relevant to Approval:**

The reader is referred to the CDTL memorandum for a full discussion of the NAI site inspections and other compliance related issues. Particularly of importance is the inspection of (b) (4), was conducted (b) (4) which has led to a regulatory action of a major amendment to this BLA. This facility is responsible for manufacturing the drug product. A 483 form was issued at the conclusion of the inspection for observations related to (but not limited to) (b) (4)

The 483 items were sufficiently serious to rise to a classification of official action indicated (OAI).

FDA exercised its right to enforce a major amendment due to the compliance issues and in response, Alexion on September 4, 2015 communicated their concerns with this action and communicated that they “have a proposed a strategy for oversight and batch certification that represents a viable solution, has agency precedent, and allows FDA to take action on the BLA now.” The FDA exercised its Major amendment on September 4, 2015 and the firm communicated publically in this regard. They stated: “Alexion Pharmaceuticals, Inc. (NASDAQ: ALXN) announced today that the U.S. Food and Drug Administration (FDA) has extended the Prescription Drug User Fee Act (PDUFA) date for its Priority Review of the Company’s Biologics License Application (BLA) for Kanuma™ (sebelipase alfa), an investigational enzyme replacement therapy for the treatment of lysosomal acid lipase deficiency (LAL-D). The previously disclosed September 8, 2015 PDUFA date has been extended by the standard extension period of three months. In response to a recent request from the FDA, Alexion submitted additional Chemistry, Manufacturing and Controls (CMC) information. Due to the timing of this submission, the FDA extended the PDUFA date to allow additional time for review of the new information. The FDA has not asked for additional clinical data.”<sup>6</sup>

## **12. Labeling**

### **Proprietary Name**

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<sup>6</sup> Public Statement, Alexion Pharmaceuticals, Alexion Receives Notification of PDUFA Date Extension for Kanuma™ (sebelipase alfa). September 4, 2015.

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.

## **Labeling Consults and Reviews**

### **Specific Labeling Issues**

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 [REDACTED] (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  $\geq 18$  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) included a general statement on larger 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 [REDACTED] (b) (4)

## 13. Decision/Action/Risk Benefit Assessment

### 13.1 Regulatory Action:

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

- 1) Kanuma is approved [REDACTED] (b) (4) for the treatment of pediatric and adult patients with lysosomal acid lipase (LAL) deficiency (i.e., cholesteryl ester storage deficiency [CESD]).

The product has a favorable risk/benefit profile for this indication. This Signatory recommends Approval of this BLA pending clearance of all inspectional issues that are pending at the time of this review and discussed above.

### 13.2 Risk Benefit Assessment:

The data submitted support a positive risk benefit assessment for Kanuma to be approved [REDACTED] (b) (4) for the treatment of pediatric and adult patients with lysosomal acid lipase (LAL) deficiency (i.e., cholesteryl ester storage deficiency [CESD]). There is an obvious documented improvement in the survival of infants with Wolman's disease based on the comparison to historical controls obtained through a properly conducted natural history study. Despite the fact that there is still unclear optimal dosing regimen for infants particularly, the proposed dosing regimen has been proven to impact survival greatly in this fatal disease. It should be noted though that survival is not definitive as there were three deaths reported during the study (See Clinical discussion above). These deaths suggest that identifying the optimal dose is critical to ensure maximal benefit to these critically ill infants. This underlies the importance of understanding the potential ER relationship in infants with LAL deficiency. The benefit risk for the CESD population has been demonstrated with reduction in LDL-c concentration which is akin to products already approved for the treatment of hypercholesterolemia. It is in the lower range but these patients are at risk for atherosclerosis, although not as well described and likely underreported. Kanuma targets the mechanism underlying the pathophysiology of CESD. DMEP consult states: "Of the lipid parameters reported, LDL-C has the most data to support a causal relationship with atherosclerotic cardiovascular disease. A meta-analysis of statin trials estimated that each 1.0 mmol/L (~39 mg/dL) reduction in LDL-C is associated with a reduction in the rate of major vascular events, defined in the referenced publication as the first

occurrence of any major coronary event, coronary revascularization, or ischemic stroke, by ~22%. In the LAL-CL02 trial, sebelipase was associated with a decrease in LDL-C of 22%, or 35 mg/dL in the trial population. If this degree of change from statin trials could be extrapolated to sebelipase in this patient population, one could estimate approximately 20% reduction in CV risk. This is speculative, however.” The overall benefit of Kanuma for the treatment of LAL is convincing and should be approved for the indication proposed.

**Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:**

There are no requirements for postmarketing risk evaluation and mitigation strategies.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

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

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

**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 substudy 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. (b) (4)

7. Validate the (b) (4)  
If the (b) (4) is revised based on the validation study, update the BLA file accordingly.

8. The microbial retention study (b) (4)

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 (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. (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 (b) (4) 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 HPAECPAD method peaks representative of (b) (4) and establish drug containing 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.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANDREW E MULBERG

09/08/2015

Deputy Director review